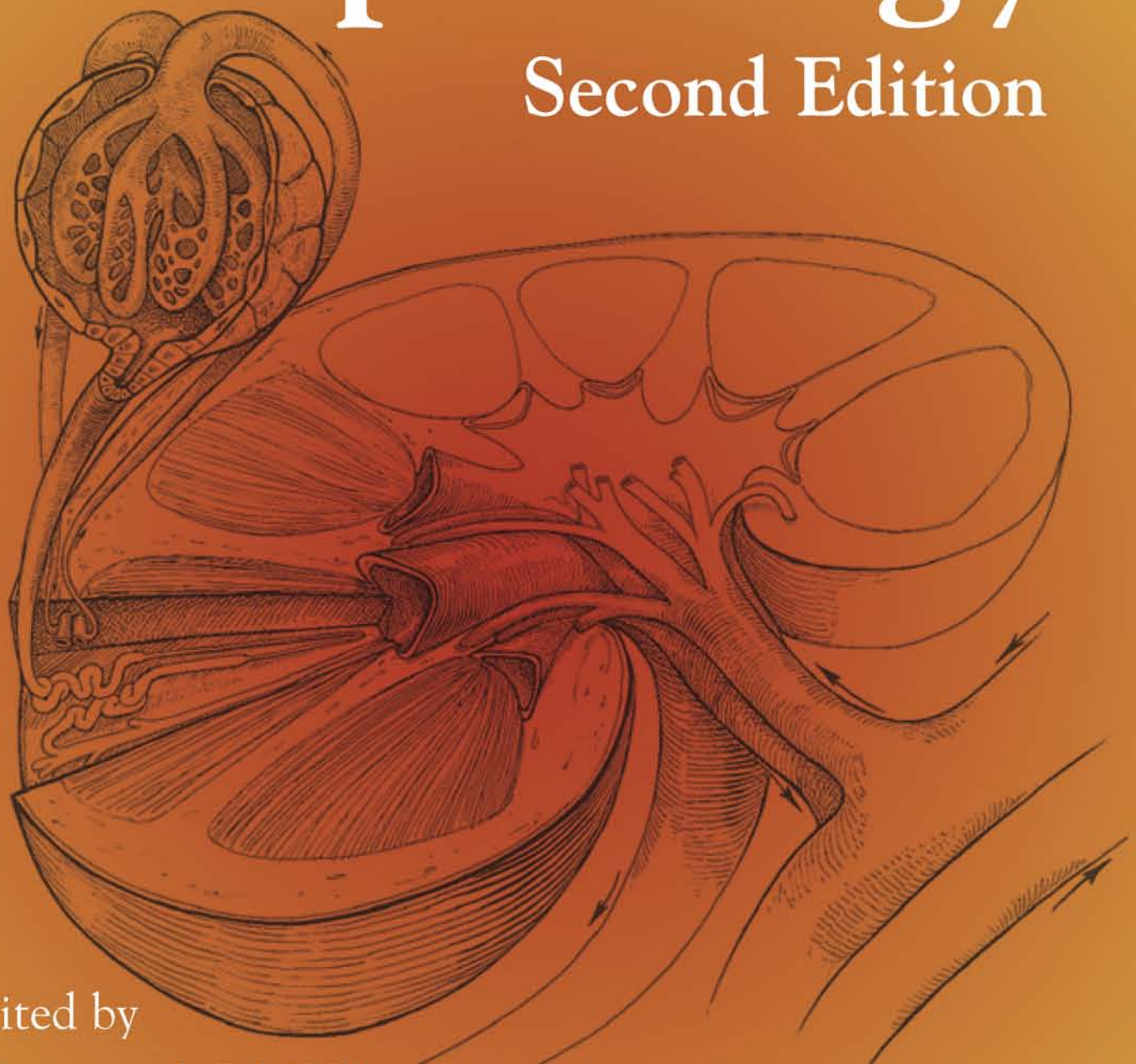
Clinical Pediatric Nephrology

Second Edition



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Preface

The first edition of *Clinical Pediatric Nephrology* was conceived as a primer of pediatric nephrology. It was devoted primarily to the clinical discussion of commonly encountered renal disorders in children, and was aimed at pediatric nephrology fellows. In addition, it was hoped that the book would be a quick source of clinically relevant information for medical students, house officers and non-nephrologists providing co-clinical care for children with kidney diseases.

The second edition of *Clinical Pediatric Nephrology* has been thoroughly updated and the book continues to emphasize the clinical implications of our present understanding of pediatric renal disorders. The authorship has been expanded to reflect the diversity of experience within the pediatric nephrology community. All of the chapters in this edition have been rewritten to reflect progress in the areas that they cover, and the number of chapters has been increased to 37. These chapters have been assigned to seven sections. The first section deals with the structure and physiology of the kidney. In addition to consideration of fluid, mineral and electrolyte handling, it includes information that is unique and essential to understanding the renal disorders that affect infants and children. Indeed, these developmentally determined responses to perturbations differentiate pediatric nephrology from the broader renal medicine. The second section addresses our assessment of the patient, as well as the context of that assessment, by considering epidemiology and the principles of diagnostic evaluation. The third section covers pathogenetic, diagnostic, and therapeutic aspects of primary and secondary parenchymal renal diseases. The fourth section elucidates renal tubular disorders, and section five discusses acute and chronic renal failure and its treatment. Hypertension is the focus of the sixth section, and the book concludes with a section or urologic problems and other surgical disorders.

While preparing such a text with friends and colleagues is a labor of love, it represents the culmination of significant efforts by all involved in the project. At the outset, we would like to thank all of the contributors who have worked within very tight deadlines to provide manuscripts for the new edition of the book. The outstanding editorial, production and marketing team at Informa Healthcare medical publishers, the new publishers of *Clinical Pediatric Nephrology,* have provided exceptional support and encouragement through all phases of this project. We are especially grateful to Robert Peden and Oliver Walter for recognizing the merits of producing a revised second edition of this book. Their personal involvement has been instrumental in the development of this book. Catriona Dixon, the Production Editor of this edition, has been a delight to work with. While valuing the constraints of time for the editors and contributors, she has skillfully managed to keep the process flowing efficiently. Her keen interest in enhancing the visual appeal of the book has been central in producing a more user-friendly format of the text, images, tables, and diagrams. Closer to home, we appreciate the assistance of Robyn Mann who provided the crucial link between the editors and the authors, and managed to get us all together for conference calls.

Each of us wishes to profoundly thank our families who have always provided a steady and stable shelter from the often distracting and sometimes stormy winds of any academic enterprise. Their selfless devotion has kept all of us well anchored and focused in our endeavor.

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Abbreviations

γ-IFN	γ-IFN
α-KG	α-ketoglutarate
A1AR	A1 adenosine receptor
AAP	American Academy of Pediatrics
ABU	asymptomatic bacteriuria
ACEI	angiotensin-converting enzyme inhibitor
ACKD	acquired cystic kidney disease
ACT	activated clotting time
ACTH	adrenocorticotropic hormone
ADA	American Diabetics Association
ADH	antidiuretic hormone
ADHD	attention deficit hyperactivity disorder
ADPKD	autosomal dominant polycystic kidney disease
AFP	α-fetoprotein
AG	anion gap
AGN	acute postinfectious glomerulonephrosis (glomerulonephritis)
AHG	anti-human globulin
AIDS	acquired immunodeficiency syndrome
AL	Alport's syndrome
ALL	acute lymphoblastic leukemia
AME	apparent mineralocorticoid excess
AMR	antibody-mediated rejection
ANA	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibodies
ANP	atrial natriuretic protein, acyclic nucleoside phosphonate
anti-dsDNA	anti-double-stranded DNA
anti-GBM	anti-glomerular basement membrane
APCs	antigen-presenting cells
APD	automated peritoneal dialysis
APN	acute pyelonephritis
APRT	adenine phosphoribosyl transferase
APSGN	poststreptococcal glomerulonephrosis
aPTT	activated partial thromboplastin time
AR	acute rejection
ARA	angiotensin receptor antagonist
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
ARPKD	autosomal recessive polycystic kidney disease
ATF	atrial natriuretic factor
ATIN	acute tubulointerstitial nephritis
ATN	acute tubular necrosis
AV	arteriovenous
AVF	arteriovenous fistula
AVG	arteriovenous graft
AVN	avascular necrosis
BFN	benign familial hematuria
BFR	blood flow rate
BFU-E	burst-forming unit-erythroid
BMI	body mass index
BOR	branchial-oto-renal syndrome
BPCA	Best Pharmaceuticals for Children Act
BPH	benign prostatic hypertrophy
BSA	body surface area
BUN	blood urea nitrogen
BWS	Beckwith–Wiedemann syndrome
CA	carbonic anhydrase
CAH	congenital adrenal hyperplasia
CAN	chronic allograft nephropathy
CAPD	continuous ambulatory peritoneal dialysis
CAT	computerized axial tomography
CAVH	continuous arteriovenous hemofiltration
CAVHD	continuous arteriovenous hemodialysis
CAVHDF	continuous arteriovenous hemodiafiltration
CBC	complete blood count
C_{Cr}	creatinine clearance
CCCK	clear cell carcinoma of the kidney
CCT	cortical collecting tube
CDK	cyclin-dependent kinase
CFU	colony-forming unit
CHF	congestive heart failure
CIC	clean intermittent catheterization
cIMT	carotid artery intimal-medial thickness
C_{In}	inulin clearance
CKD	chronic kidney disease
CKiD	Chronic Kidney Disease in Children Study
CMV	cytomegalovirus
CNM	congenital mesoblastic nephroma
CNS	as in Finnish congenital nephrotic syndrome
CNS	central nervous system
CP	cerebral palsy
CPB	cardiopulmonary bypass
CPD	continuous peritoneal dialysis
CR	chronic rejection
CRF	chronic renal failure
CRI	chronic renal insufficiency
CRIC	Chronic Renal Insufficiency Cohort Study
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
CT	computed tomography
CTIN	chronic tubulointerstitial nephritis
CVD	cardiovascular disease
CVP	central venous pressure
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
DASH	Dietary Approaches to Stop Hypertension
DDS	Denys–Drash syndrome
DES	dysfunctional elimination syndrome
DFNA	autosomal dominant deafness

DFS	daytime frequency syndrome
DGF	delayed graft function
DKA	diabetic ketoacidosis
DMSA	dimercaptosuccinic acid (Tc 99m DMSA)
DRI	dietary reference intake
DRTA	distal renal tubular acidosis
DTT	dithiothreitol
EACA	epsilon-aminocaproic acid
EAR	estimated average requirement
EBV	Epstein–Barr virus
ECF	extracellular fluid
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
EF	endothelial fenestrations
EIA	enzyme-linked immunoassay
ELISA	enzyme-linked immunosorbant assay
ELNT	Euro-Lupus Nephritis Trial
ENaC	epithelial sodium channel
EPO	erythropoietin
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ESRF	end-stage renal failure
ESWL	extracorporeal shock wave lithotripsy
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FE	fractional excretion
FENa	fractional excretion of sodium
FGF	fibroblast growth factor
FGGS	focal global glomerulonephrosis
FH	favorable histology
FISH	fluorescence in-situ hybridization (test)
FRNS	frequently relapsing nephrotic syndrome
FSGS	focal segmental glomerulosclerosis
GBM	glomerular basement membrane
GCKD	glomerulocystic kidney disease
GDNF	glia derived neurotrophic factor
GFR	glomerular filtration rate
GH	growth hormone
GHR	growth hormone receptors
GI	gastrointestinal
GN	glomerulonephritis
GRA	glucocorticoid-remediable aldosteronism
GRE	glucocorticoid response element
HAART	highly active antiretroviral therapy
HAR	hyperacute rejection
HbF	fetal hemoglobin
HBV	hepatitis B virus
HCMA	hyperchloremic metabolic acidosis
HCV	hepatitis C virus
HD	hemodialysis
HDL	high-density lipoprotein
HGF	hepatocyte growth factor
HIT	heparin-induced thrombocytopenia
HIV-1	human immunodeficiency virus
HLA	human leukocyte antigen
HNF	hepatocyte nuclear factor
hpf	high-power field
HPLC	high-performance liquid chromatography
HPRT	hypoxanthine–guanine phosphoribosyl transferase
HRQOL	health-related quality of life
HSP	Henoch–Schönlein purpura
HSPN	Henoch–Schönlein purpura nephritis
HUS	hemolytic uremic syndrome
iCa^{2+}	circuit ionized calcium
ICAM 1	intercellular adhesion molecule 1
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus (type 1 diabetes)
IEP	individualized educational program
IF	immunofluorescence
IFA	immunofluorescence microscopy assay
Ig	immunoglobulin
IgAN	IgA nephropathy
IGF	insulin-like growth factor
IGF-1	insulin-like growth factor-1
IL	interleukin: e.g. IL-6
IMA	immunoradiometric assay
IMCT	inner medullary collecting tube
IMPDH	inosine monophosphate dehydrogenase
IPD	intermittent peritoneal dialysis
IPP	intraperitoneal pressure
IPPR	International Pediatric Peritonitis Registry
ISKDC	International Study of Kidney Disease in Children
IV	intravenous
IVIg	intravenous immunoglobulin
IVP	intravenous pyelogram (pyelography)
IVU	intravenous urography
K/DOQI	Kidney Disease Outcome Initiative
KUB	Kidneys, Ureter, Bladder
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LDN	laparoscopic donor nephrectomy
LVH	left ventricular hypertrophy
MARS	molecular absorbents recirculation system
MCD	medullary cystic disease
MCDK	multicystic dysplastic kidney
MCKD	medullary cystic kidney disease
MCNS	minimal change nephrotic syndrome
MCR-1	monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MesPGN	mesangial proliferative glomerulonephrosis
MGN	membranous glomerulonephrosis (glomerulonephritis)
MMF	mycophenolate mofetil
MODS	multi-organ dysfunction syndrome
MODY	maturity-onset diabetes of the young
MPA	microscopic polyangiitis

MPA	mycophenolic acid
MPGN	membranoproliferative glomerulonephrosis (glomerulonephritis)
MPO	myeloperoxidase
MPPY	million persons per year
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MSK	medullary sponge kidney
MTAC	mass transfer area coefficient
mTOR	molecular target of rapamycin
NAE	net acid excreted
NAPRTCS	North American Pediatric Renal Transplant Cooperative Study
NCDS	National Cooperative Dialysis Study
NFAT	nuclear factor activating transcription
NGAL	neutrophil gelatinase-associated lipocalin
NHANES	National Health and Nutrition Examination Survey
NICU	neonatal intensive care unit
NIH	National Institutes of Health
NKF	National Kidney Foundation
nPCR	normalized protein catabolic rate
NPH	nephronophthisis
nPNA	normalized protein equivalent of nitrogen appearance
NPS	nail-patella syndrome
NR	nephrogenic rests: ILNR – intralobular; PLNR – perilobular
NRTI	nucleoside reverse transcriptase inhibitor
NSAIDs	non-steroidal anti-inflammatory drugs
NWTSG	National Wilms' Tumor Study Group
OAB	overactive bladder
ODN	open donor nephrectomy
OMCT	outer medullary collecting tube
OPO	organ procurement organization
OPTN	Organ Procurement and Transplantation Network
PAH	*p*-aminohippurate
PAIs	pathogenicity islands
PCNL	percutaneous nephrolithotomy
PCP	*Pneumocystis carinii* pneumonia
PCR	polymerase chain reaction
PCR	protein catabolic rates
PCTA	percutaneous transluminal angioplasty
PD	peritoneal dialysis
PEPCK	phosphoenolpyruvate carboxykinase
PET	peritoneal equilibration test
PET	positron emission tomography
PG	prostaglandin
PHA	pseudoaldosteronism (e.g. PHAI, PHAII)
PI	paradoxical incontinence
PNE	primary nocturnal enuresis
POR	parent of origin
ppCRRT	Prospective Pediatric CRRT
PPD	purified protein derivative
PPDSC	Pediatric Peritoneal Dialysis Study Consortium
PR3	proteinase 3
PRA	panel reactive antibodies
PRA	plasma renin activity
PRISM2	Pediatric Risk of Mortality 2
PRPS	phosphoribosyl pyrophosphate synthetase
PRTA	proximal renal tubular acidosis
PTFE	polytetrafluoroethylene
PTH	parathyroid hormone
PTLD	post-transplant lymphoproliferative disorder
PUV	posterior urethral valves
PVB19	human parvovirus 19
RA	rheumatoid arthritis
RAAS	renin–angiotensin–aldosterone system
RAS	renal artery stenosis
RAS	renin–angiotensin system
RBCs	red blood cells
RBUS	renal bladder ultrasonography
RCC	renal cell carcinoma
RCTs	randomized controlled trials
RDA	recommended daily allowance
rhGH	recombinant human growth hormone
RNC	radionuclide crystography
RO	reverse osmosis
ROMK	rat outer medulla potassium
ROS	reactive oxygen species
RPD	renal pelvic diameter
RPF	renal plasma flow
RPGN	rapidly progressive (proliferative) glomerulonephrosis
RPN	renal papillary necrosis
RR	relative risk
RRF	residual renal function
RRT	renal replacement therapy
RTA	renal tubular acidosis
RTK	rhabdoid tumor of the kidney
RVH	renovascular hypertension
SCD	sickle cell disease
SCUF	slow continuous ultrafiltration
SD	slit diaphragm
SDNS	steroid-dependent nephrotic syndrome
SDS	standard deviation score
SEP	sclerosing encapsulating peritonitis
SIADH	syndrome of inappropriate secretion of diuretic hormone
SIOP	International Society of Paediatric Oncology
SIRS	soluble immune response suppressor
SLE	systemic lupus erythematosus
SPAD	single-pass albumin dialysis
SPECT	single-photon emission computed tomography
SPI	selectivity of proteinuria index
SPNSG	Southwest Pediatric Nephrology Study Group
SRINS	steroid-responsive idiopathic nephrotic syndrome

SRNS	steroid-resistant nephrotic syndrome
SRTR	Scientific Renal Transplant Registry
SSNS	steroid-sensitive nephrotic syndrome
STAT	signal transducer and activator of transcription
Stx	Shiga toxin
SVA	small-vessel vasculitis
TA	titratable acid
TAL	thick ascending limb (of loop of Henle)
TBM	tubular basement membrane
TEC	tubular epithelial cells
TGF-β_1	transforming growth factor-β_1
THP	Tamm–Horsfall protein
TIN	tubulointerstitial nephritis
TINU	tubulointerstitial nephritis with uveitis
TMA	thrombotic microangiopathy
TMA	transplant microangiopathy
TNF-α	tumor necrosis factor-α
TNTC	too numerous to count
TP	tubular phosphate reabsorption
tPA	tissue plasminogen activator
TPN	total parenteral nutrition
TSAT	transferrin saturation
TSH	thyroid-stimulating hormone
TTKG	transtubular potassium gradient
TTP	thrombotic thrombocytopenic purpura
UAC	umbilical arterial catheter
UNOS	United Network for Organ Sharing
Up/c	urine protein to creatinine
UPEP	urine protein electrophoresis
UPJ	ureteropelvic junction
URI	upper respiratory infection
URR	urea reduction ratio
US	ultrasound
USRDS	United States Renal Data System
UTI	urinary tract infection
UUO	unilateral ureteral obstruction
UVJ	ureterovesical junction
VACTER	Vertebral, Anal atresia, Tracheoesophageal fistula, Radial and Cardiac
VCUG	voiding cystourethrography
VEGF	vascular endothelial growth factor
VLDL	very low-density lipoprotein
VPGF	vascular permeability growth factor
VUR	vesicoureteral reflux
vWF	von Willebrand factor
VZIG	varicella zoster immunoglobulin
WBCs	white blood cells
WT	Wilms' tumor
Z-BUF	zero-balance ultrafiltration

Part 1

Kidney – structure and applied renal physiology

1 Structure and development of the kidney

Norman D Rosenblum

Kidneys, a vital organ system, evolve in a complex fashion during intrauterine development. Functional development of the kidneys is incomplete at birth, even in the full-term infants, and normal renal function is not achieved until approximately 2 years of age. The deficit in renal function is further magnified in pre-term infants. Developmental abnormalities of the urinary tract are common and account for 30–50% cases of end-stage renal disease in children. The objectives of this chapter are to explore the structure and a current understanding of development of the urinary tract.

Structure of the kidneys

Human kidneys are two bean-shaped structures that are located in the paravertebral retroperitoneal space. At birth, each kidney measures 4–4.5 cm in length. Each adult kidney weighs 115–170 g, and measures 10–11.5 cm in length and 5–7 cm in width. The right kidney is placed slightly lower as compared to the left side. The superior pole of each kidney is in contact with the adrenal gland and the anterior surface lies in relation to duodenum on the right side and the pancreas on the left side. Variable portions of colon may be in contact with the inferior pole of the anterior surface of the kidneys, and on the left side spleen wraps the anteriolateral aspects of the upper half of the kidney. Posteriorly, the kidney lies in relation to the muscles of the back, including the psoas. The 12th rib and a portion of the 11th rib usually cover the upper third of the posterior surface of the left kidney, while the 12th rib barely reaches the upper pole of the right kidney in most individuals. The outer surface of the kidney is smooth in normal adults, but a lobular appearance is common in newborns and infants (fetal lobulations). A thin but firm capsule, which can be easily stripped, covers the outer surface of the kidney.

The ureter and renal vessels are placed in the medial side of the kidney known as the hilum. The cut surface of the kidney (Figure 1.1) demonstrates that the hilum of the kidney opens into central space, termed the renal sinus. The renal sinus contains the renal pelvis, calyces, and the branching renal vessels. The pelvis of the kidney extends out of the kidney to form ureter, while in the intrarenal portion divides into numerous calyces (6–10 in number), which drain the renal pyramids (see above). A distinct outer cortex and an inner

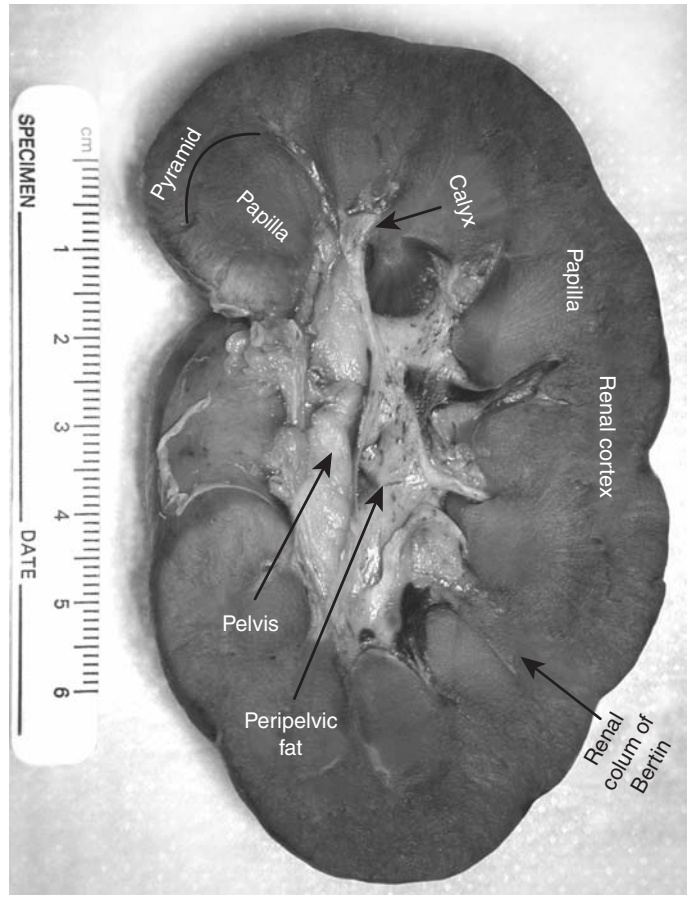

Figure 1.1 Cut surface of a normal kidney of a child showing anatomic landmarks. (Photograph courtesy of Ronald M Przygodzki MD.)

medulla are noted on sectioning the kidney. The medulla is arranged in several conical structures called renal pyramids, with the apex directed to the inner aspect of the kidney and the base towards the renal cortex. The tips of the renal pyramids (known as papillae) open directly into the calyces. The cortex of the kidney is lighter in color as compared to medulla. The area of the renal cortex that fills the space between two medullary pyramids is known as renal columns (of Bertini).

Microscopic features

The human kidney consists, on average, of one million nephrons. This number varies considerably among individuals. A smaller numerical endowment of nephrons is hypothesized to be a risk factor for renal-related morbidity, especially hypertension, during adult life.[1] Each nephron consists of a glomerulus connected to a tubule that is, in turn, connected to a collecting duct (Figure 1.2). Three types of nephrons are identified based on their location either in the superficial cortex, mid-cortex, or juxtamedullary region.

The nephron can be broken down into several units. The glomerulus consists of a complex arrangement of cells and extracellular matrices (Figure 1.3). Glomerular structures function together to generate a glomerular filtrate that enters the urinary (Bowman) space bounded on the outside of the glomerulus by Bowman capsule. Influx of blood into glomerular capillaries is via the afferent arteriole. Efflux of blood is via the efferent arteriole. From Bowman space to the capillary, the order of cells and structures is: Bowman capsule, parietal epithelial cells, Bowman space, podocytes, the glomerular basement membrane (GBM), and capillaries. The mesangium consists of the mesangial cells and their secreted matrix, the mesangial matrix, and is interposed between the capillaries. Filtration of molecules across this structural barrier is limited by size, shape, and charge. Charge selectivity is determined by negatively charged molecules present on each component of the filtration barrier. Size selectivity is determined by the GBM and, to a greater extent, by the slit diaphragm generated by interposing podocyte foot processes.

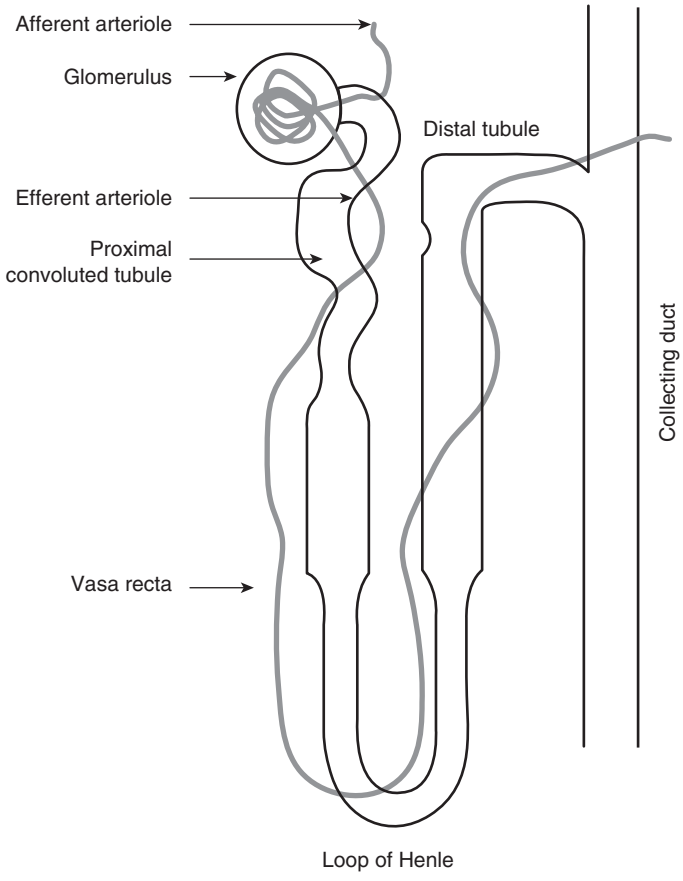

Figure 1.2 A schematic diagram of a nephron. Note that the efferent arteriole feeds the vasa recta.

The glomerular filtration barrier consists of the podocyte, glomerular basement membrane, and the glomerular capillary (Figure 1.4). Podocytes, also termed visceral epithelial cells, exist between the capillaries and the urinary space, and envelop the capillaries and the mesangium. Podocyte bodies elaborate cellular extensions that end as foot processes opposed to the GBM (Figure 1.5). The foot processes of adjacent podocytes interdigitate forming the slit diaphragm (see Figure 1.4A). The luminal aspect of the podocyte membrane and the slit diaphragms are negatively charged due to the presence of sialoglycoproteins. The GBM forms the middle layer of the filtration barrier. As imaged by electron microscopy, the GBM appears as a trilaminar structure consisting of a lamina densa interposed between lamina rarae on the podocyte and endothelial sides (Figure 1.4). In reality, such distinct geographic segregation may not exist; these observations may be a fixation artifact. The GBM is made of a multicomponent extracellular matrix. The major components of the GBM are type IV collagen, laminin, and heparan sulfate proteoglycans. The expression of particular members of these large molecular families is somewhat restricted to the GBM. Current models of GBM structure suggest that it consists of type IV collagen modules connected in an end-to-end, as well as side-to-side fashion to form a complex three-dimensional network with connections to other resident proteins and proteoglycans. Endothelial cells line the inner aspect of the GBM. In contrast to endothelial cells in nonrenal tissues, glomerular endothelial cells are separated by pores 50–100 nm in diameter. These pores are known as endothelial fenestrations. Decoration of the luminal endothelial membrane with polyanionic glycoproteins together called the glycocalyx generates a negatively charged barrier that limits filtration of plasma proteins across these pores.

The mesangium consists of the mesangial cell, a 'mesenchymal'-appearing cell that lacks apical-basolateral polarity observed in differentiated epithelial cells. An extracellular matrix, termed the mesangial matrix surrounds mesangial cells. The composition of this matrix is generally distinct from that of the GBM. Whereas members of the collagen, laminin, and proteoglycan families are contained within the mesangium, the particular family members differ between the GBM and the mesangial matrix. Mesangial cells extend cellular processes that attach to

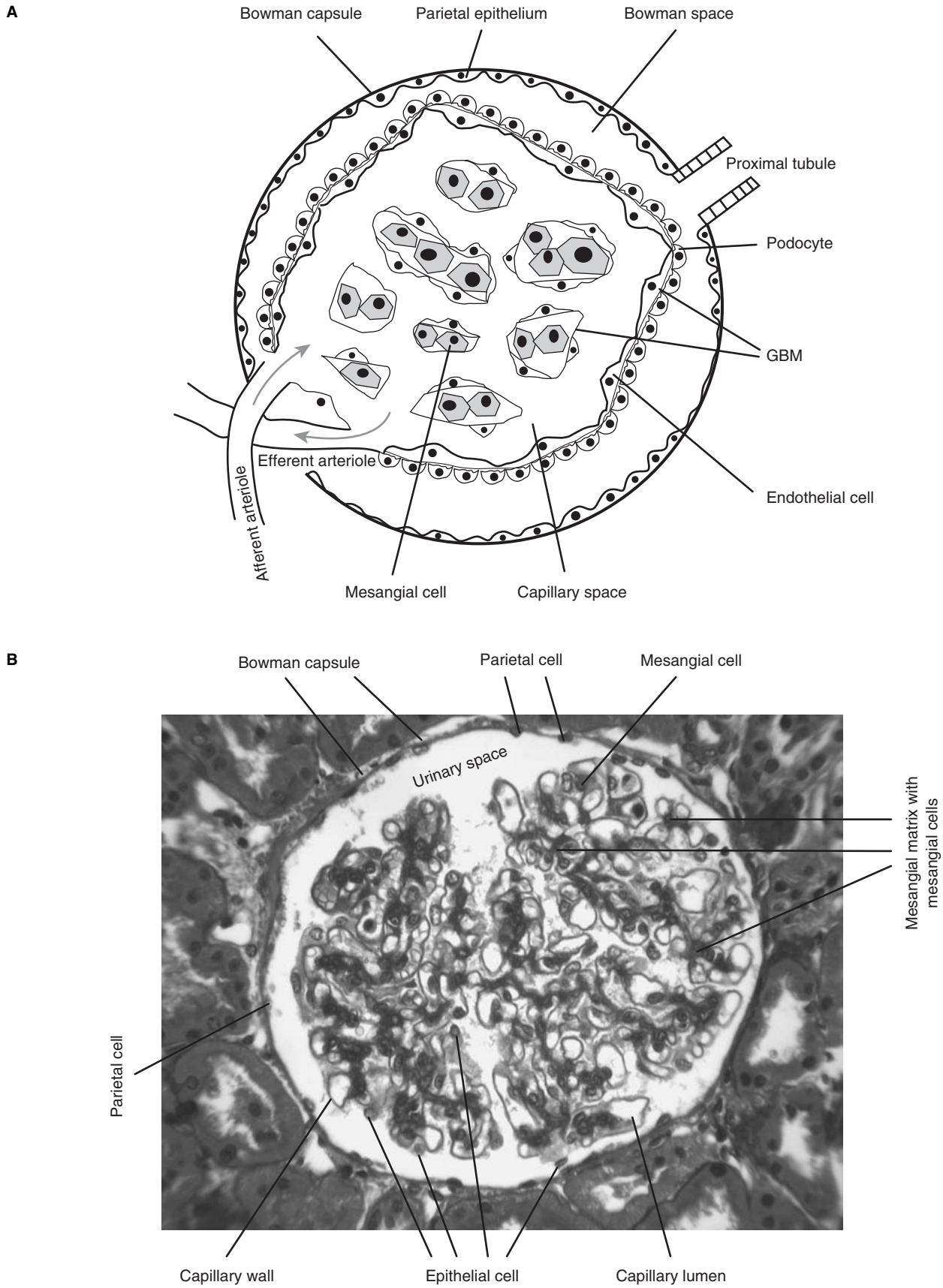

Figure 1.3 The normal glomerulus. (A) A schematic diagram showing the various cell types of the glomerular structure. GBM, glomerular basement membrane. (B) Light microscopy of a glomerulus histologic architecture of the glomerulus.

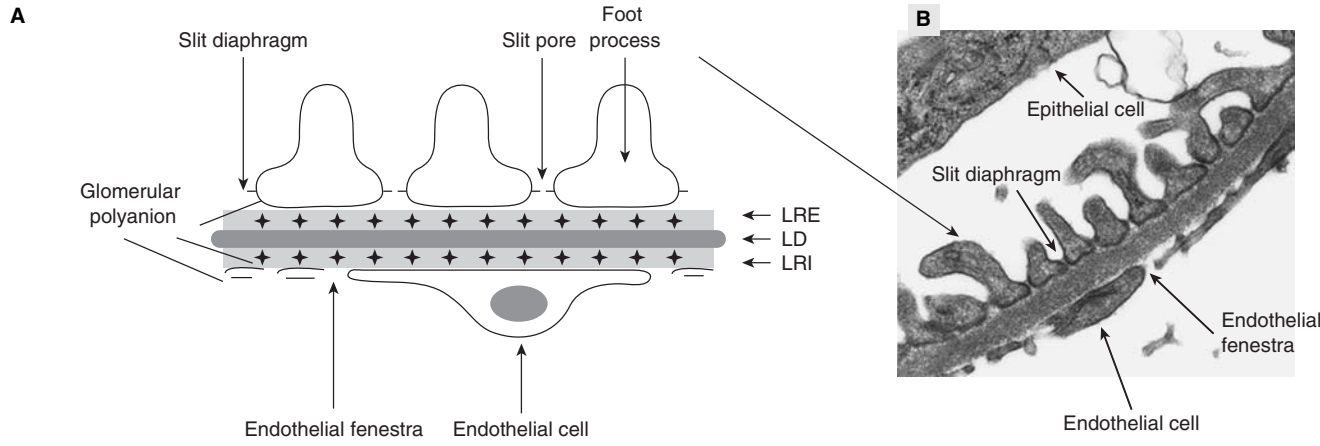

Figure 1.4 The glomerular filtration barrier. (A) Schematic representation showing an endothelial cell; the lamina rara interna (LRI), lamina densa (LD), and lamina rara externa (LRE) of the glomerular basement membrane (GBM), epithelial foot processes, and glomerular polyanion. The polyanion coats the endothelial and epithelial cells and is also present at regular intervals in the GBM. (B) An electron micrograph of the normal filtration barrier. (Photomicrograph courtesy of Fermin Tio MD.)

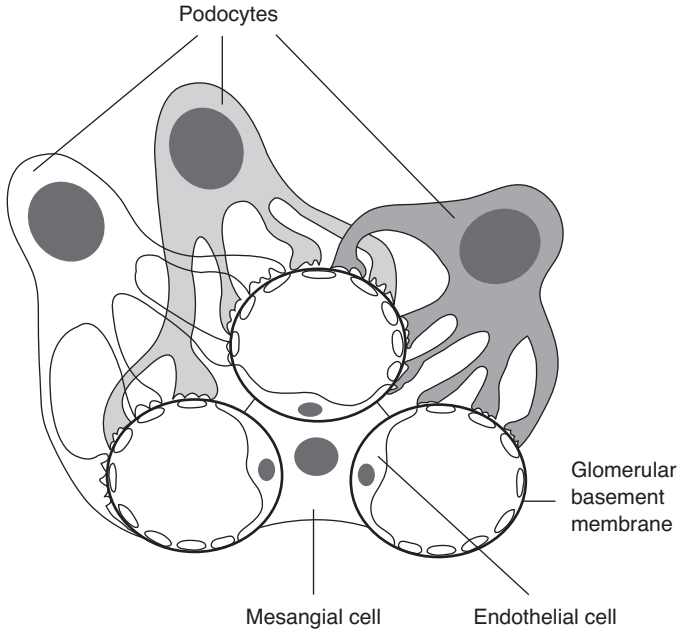

Figure 1.5 A schematic diagram showing physical relationships among podocytes and capillaries. Note that processes from different podocytes can contribute to the foot processes adjacent to each capillary.

the GBM such that changes in mesangial cell shape are transduced to the glomerular tuft.

Within each nephron, a tubule extends from the glomerulus to the renal papilla. The tubule is functionally and morphologically subdivided into the proximal tubule, the descending and ascending aspects of the loop of Henle, the distal tubule, and the collecting duct. The renal tubule consists of a single layer of epithelial cells; these cells are attached to the tubular basement membrane along their basal side. The apical aspect of these cells projects into the tubular lumen, and remains in contact with the tubular fluid. The morphologic appearance of the epithelial cell resident in each tubular segment varies and is determined by the functional attributes of the tubular segment. For example, the brush border of proximal tubule cells is extensive and highly redundant, giving it a large surface area in the tubular lumen, which is consistent with the high-capacity reabsorptive function of the proximal tubule.

Within the kidney, two patterns of renal artery branching are recognized. Most commonly, an anterior and a posterior division are present. The anterior division branches to form four segmental arteries, whereas the posterior division gives rise to one segmental division. The segmental arteries do not form anastomoses with each other. Each segmental artery gives rise to interlobar arteries, which extend toward the cortex on either side of a renal pyramid. At the junction between cortex and medulla, the interlobar arteries divide dichotomously into arcuate arteries that branch through the cortex, finally terminating as afferent arterioles. The intrarenal veins exist in parallel to the arteries, although they are more highly interconnected. The medulla is supplied by efferent arterioles of the juxtamedullary glomeruli that form a venous plexus around the tubules.[2]

Renal development

In mammals, the kidneys develop in three stages, from rostral (head end) to caudal (rump end) – the pronephros, the mesonephros, and the metanephros (permanent kidney). The pronephros is rudimentary and nonfunctional. The mesonephros functions briefly and then involutes toward the end of the first trimester. The metanephros does not involute and becomes the permanent kidneys. The metanephros begins to develop during the fifth week of gestation (E5 weeks) and urine generation is initiated around E10 weeks. During fetal life, the kidneys are lobulated, and a lobular appearance is present even at birth. Thereafter, the external kidney surface becomes smooth as the kidney grows.

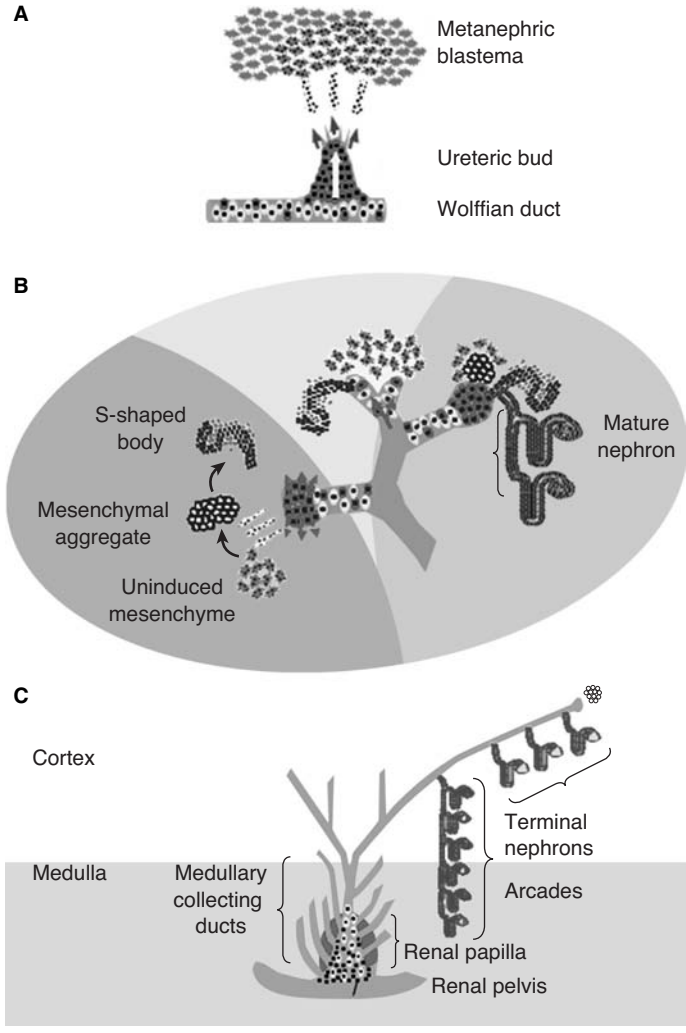

Figure 1.6 Stages of renal morphogenesis. (A) Ureteric bud outgrowth from the Wolffian duct is modulated by factors secreted by the metanephric blastema and the mesoderm surrounding the duct. (B) Morphologic intermediates formed during nephrogenesis. The uninduced mesenchyme is induced to form a mesenchymal aggregate, which forms a comma-shaped (not shown) and then an S-shaped body. Morphologic intermediates at various stages of development are shown in association with different ureteric bud tips. (C) Patterning of the kidney into a cortex and medulla. The cortex consists of nephrons with short and long tubular (Henle's) loops and collecting ducts that connect to the distal tubules. The medulla consists of the tubules from long loops of Henle and collecting ducts which terminate in the papillae.

Initially, the kidneys lie adjacent to each other in the pelvis, and the hilum of each faces ventrally (towards the anterior abdominal wall). As the trunk grows, the kidneys come to lie higher in the abdomen and farther apart. In addition, the hilum rotates almost 90°. By E9 weeks, the kidneys attain their adult positions. Malrotation and ectopic kidney location is due to abnormal rotation and ascent, respectively. Failure of the kidneys to migrate upwards from the pelvis results in the formation of pelvic kidneys. These kidneys are usually positioned close to each other and may fuse in some cases to give rise to a *pancake* kidney. In about 1 in 500 individuals, the inferior poles fuse prior to ascent, generating a *horseshoe kidney*.

At the earliest stage of kidney formation, the renal arteries are derived as branches of the common iliac arteries. As the metanephroi ascend, they receive branches from the distal aorta, then from the abdominal aorta. Normally, the distal branches disappear and the abdominal branches become the permanent renal arteries. Variations in the arterial supply are common and reflect the changing nature of the arterial supply during fetal life. While the majority of individuals have a single renal artery, about 25% have two to four.[3]

Metanephric development

As indicated above, metanephric induction occurs at E5 weeks, at a time when the ureteric bud is induced to grow out from the Wolffian (nephric) duct and invade the metanephric blastema (Figure 1.6A). The blastema comprises a heterogeneous population of cells including mesenchymal cells, that will be transformed to epithelial glomerular and tubular progenitors and stromal cells that support the formation of glomerular and tubular elements. Under the direction of growth factor-mediated signals elaborated by the metanephric mesenchyme, the ureteric bud undergoes repetitive growth and branching events, a process termed branching morphogenesis (Figure 1.6B). In general, each branch divides to form two daughter branches, creating generations of ureteric bud branches. In reciprocal fashion, the ureteric bud induces the mesenchyme adjacent to each bud tip to develop through a stereotypic sequence of structures consisting of mesenchymal condensates, pretubular aggregates, renal vesicles, and comma- and S-shaped bodies. At one end of the S-shaped body, a layer of epithelial cells will give rise to future podocytes. The basal aspect of these cells rests on the future glomerular basement membrane. A cleft between the podocytes and the cells that will become the proximal tubule exists on the other side of the basement membrane. Endothelial and mesangial cells migrate into this cleft. On the other side of the podocytes are cells that will become parietal epithelial cells. Initially, each branch of the ureteric bud and its daughter collecting ducts induces formation of one nephron.

Formation of 15 generations of ureteric buds/collecting ducts induces an identical number of nephrons. The remaining nephrons form by induction of approximately 10 nephrons around the stem of an elongating ureteric bud/collecting duct branch. The connecting tubules of each of these nephrons then attach to the stem of the collecting duct branch in series to form an arcade (Figure 1.6C). After formation of arcades, the terminal branch of the 15th generation begins to elongate and to develop a succession of ampullae that induce nephrons on each side of the terminal branch. During the latter stages of kidney development, tubular segments formed from the first five generations of ureteric bud branching undergo remodeling to form the pelvis and calyces.

Molecular control of development

During embryogenesis, formation of tissues is controlled by one or more morphogenetic pathways that consist of a hierarchy of control elements integrated within a circuit (Figure 1.7). An ever-expanding body of knowledge has been generated by the study of renal development in experimental models, most notably the mouse, a paradigm for human kidney development. Development is initiated by the activity of one or more genes that control the behavior(s) of target cells. These cells are either those in which the genes are themselves expressed or neighboring cells. Target cells are instructed to engage in a repertoire of activities that include proliferation, programmed cell death (apoptosis), movement, shape change, or alteration in their interactions with extracellular matrices. One or more of these changes in cell behavior influences the manner in which a particular three-dimensional structure (e.g. a collecting duct) is constructed. In turn, changes in cell behavior and structural architecture affect gene expression, thereby creating a feedback mechanism that serves to instigate subsequent morphogenetic events and, finally, maintain tissue architecture. In the section that follows, molecular aspects of morphogenetic pathways that control formation of renal tissue elements are highlighted. This is followed by a discussion of genes mutated in individuals with renal hypoplasia and dysplasia and the functions of these genes.

Control of ureteric bud outgrowth

Outgrowth of the ureteric bud from the Wolffian duct is controlled by genes expressed in either the ureteric bud or metanephric blastema, or simultaneously, in both these tissues.[4] These genes function within a morphogenetic pathway (Figure 1.8). Genes expressed in the metanephric blastema that are required for ureteric bud outgrowth include the transcription factors *Pax2* and *Eya1*, the secreted growth factor glia cell derived neurotrophic factor (GDNF), and the GNDF cell surface receptor, RET. Studies in mice have identified genes that function upstream of *Gdnf* to limit or promote its expression, thereby controlling ureteric bud outgrowth. These studies have identified *Pax2* as a positive regulator of *Gdnf*.[5] Absence of *Gdnf* expression in the metanephric mesenchyme of *Eya1* deficient mice demonstrates that *Eya* also controls *Gdnf*.[6] Homozygous deficiency of *Pax2*, *Eya1*, *Gdnf*, or *Ret* in mice causes failure of ureteric bud outgrowth and bilateral renal agenesis or severe renal dysgenesis, with variable penetrance depending on the gene involved. Identical phenotypes have been observed in mice deficient in heparan sulfate 2-sulfotransferase,[7] demonstrating a critical role for heparan sulfate in mediating interactions between the ureteric bud and the metanephric blastema.

During kidney development, the site of ureteric bud outgrowth is invariant and the number of outgrowths is limited to one. It is believed that outgrowth of a single ureteric bud at the appropriate position is controlled by mesenchymal factors that restrict the location of ureteric bud outgrowth. Further, it is

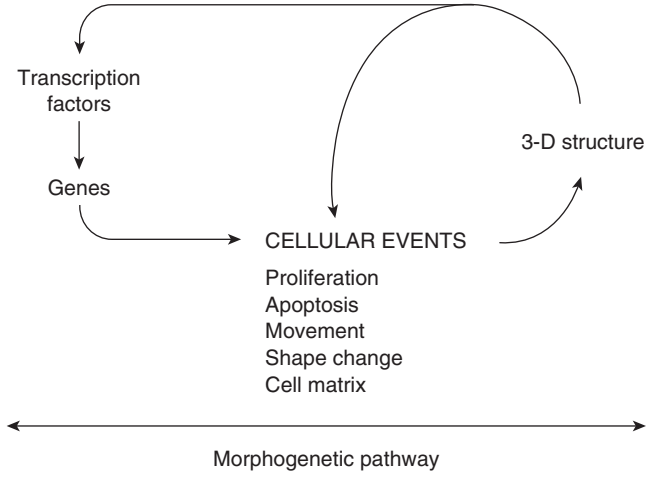

Figure 1.7 A morphogenetic pathway. Gene products control a circumscribed set of cellular events. Changes in cell behavior determine the three-dimensional (3-D) structure of tissue elements. Changes in cellular behavior also generate changes in gene expression, thus generating an integrated feedback loop that regulates gene expression.

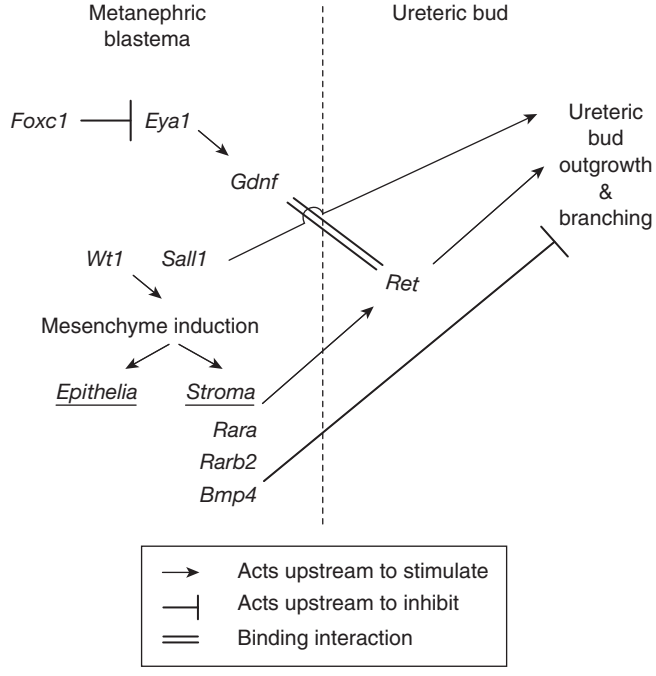

Figure 1.8 Morphogenetic pathway for ureteric bud branching. Products of genes expressed in the metanephric mesenchyme and ureteric bud interact to control ureteric bud outgrowth and branching. *Wt1* maintains the viability and competency of the metanephric mesenchyme at the onset of metanephric development. Positive regulators of ureteric bud outgrowth and branching include *Gdnf*, *Ret,* and *Sall1*. Inhibition of *Gdnf* expression by *Foxc1* limits the domain of GDNF expression, thereby regulating ureteric bud outgrowth. *Gdnf* and *Ret* are positively regulated by *Eya1* and *RARs,* respectively. *Bmp4* works via a parallel pathway to inhibit ureteric bud outgrowth.

suggested that the site of ureteric bud outgrowth determines the final site of the ureter orifice in the bladder: i.e. more caudal or cranial budding from the duct can lead to a defective ureterovesical valve and urinary outflow obstruction as well as aberrant insertion of the ureteric bud into the metanephric mesenchyme, resulting in renal dysplasia. *Foxc1* (also known as *Mf1*), a forkhead/winged helix transcription factor, is expressed in a similar metanephric domain to *Gdnf* during embryonic development. Homozygous *Foxc1* null mutant mice exhibit renal abnormalities consisting of ureteric duplication, hydroureter, and ectopic ureteric buds, suggesting that *Foxc1* negatively controls the domain of *Gdnf* expression.[8] Indeed, anterior expansion in the spatial expression domain of *Eya1* and *Gdnf* in *Foxc1* null mice is consistent with this concept. BMP4 is expressed in the mesenchyme surrounding the Wolffian duct. The presence of ureter duplication in some *Bmp4* heterogygous mice suggests that BMP4 inhibits ureter branching.[9] Thus, ureteric bud outgrowth is tightly regulated by genetic pathways that promote or inhibit.

Collecting duct branching

The invariant number and spatial pattern of collecting ducts in the mature kidney suggest that branching morphogenesis is tightly regulated. In mice, fewer ureteric bud branches are formed in the posterior kidney than in the anterior kidney. This asymmetry is probably controlled, in part, by *Hox* genes originally described as regulators of body segmentation in fruit flies.[10] In addition to their critical roles during ureteric bud outgrowth, GDNF and its cognate receptors stimulate ureteric bud branching. In mice, genetic deficiency of *Gdnf* and *Ret* causes decreased ureteric bud branching. RET expression is controlled by members of the retinoic acid receptor family of transcription factors. These members, including RAR α and RAR β_2, are expressed in stromal cells surrounding *Ret*-expressing ureteric bud branch tips.[11,12] Mice deficient in these receptors exhibit a decreased number of ureteric bud branches and diminished expression of *Ret*. Two members of the fibroblast growth factor (FGF) family of signaling peptides stimulate collecting duct morphogenesis in mice. Homozygous null mutations in the *Fgf7* gene result in a reduced number of ureteric bud branches and underdevelopment of the renal papilla.[13] Mice with a homozygous null mutation in *Fgf10* also have kidneys that are smaller than those in wild-type mice and exhibit a decreased number of medullary collecting ducts, medullary dysplasia, and dilatation of the renal pelvis.[14] Thus, a repertoire of signaling pathways promotes renal branching morphogenesis.

Renal branching morphogenesis is also regulated by inhibitory signaling pathways. In mice, bone morphogenetic proteins (BMPs) signaling via their activin-like-kinase (ALK) receptors inhibit branching morphogenesis. Targeted overexpression of ALK3 in the ureteric bud lineage decreases branching morphogenesis and is associated with decreased nephron formation.[15] Deficiency of BMPs and their signaling intermediates is associated with increased branching.[16] Thus, integration of signals from these diverse and opposing pathways by ureteric bud and collecting duct cells controls branching behavior.

Formation of the calyces and pelvis

Patterning of the collecting system to form the calyces and pelvis is controlled by sonic hedgehog (SHH), members of the BMP family, and by angiotensin and its cell surface receptors. SHH is a secreted growth factor that controls cell determination and proliferation in many developmental contexts. In mice, *Shh* deficiency interferes with formation of the smooth muscle layer surrounding the upper ureter and causes dilatation of the pelvis.[17] Loss of *Bmp4* expression appears to be a pathogenetic mechanism during the genesis of hydronephrosis in these mice. Consistent with these observations, a subset of mice with spontaneous and engineered mutations in *Bmp4* and *Bmp5* demonstrate dilatation of the ureters and collecting system (ureterohydronephrosis), and ureteral bifurcation.[9,18] Mutations in the genes encoding components of the renin–angiotensin axis, best known for their role in controlling renal hemodynamics, also cause abnormalities in the development of the renal calyces and pelvis. Mice that are homozygous null for angiotensin receptor-1 (*Agtr1*) demonstrate atrophy of the papillae and underlying medulla.[19] The underlying defect appears to be a decrease in proliferation of the smooth muscle cell layer lining the pelvis, resulting in decreased thickness of this layer in the proximal ureter. Mutational inactivation of *Agtr2* results in a range of anomalies, including vesicoureteral reflux, a duplex kidney, renal ectopia, ureteropelvic junction stenosis, ureterovesical junction stenosis, renal dysplasia, renal hypoplasia, multicystic dysplastic kidney, or renal agenesis.[20] Null mice demonstrate a decreased rate of apoptosis of the cells around the ureter, suggesting that *Agtr2* plays a role in modeling of the ureter. Together, these studies highlight the role of smooth muscle patterning in the formation of the pelvic–ureteric junction.

Formation of glomerular and tubular precursors

The development of metanephric derivatives begins when the blastema is rescued from apoptosis and induced to proliferate coincident with the invasion of the ureteric bud. Expression of the Wilms' tumor 1 (*Wt1*) gene product, a transcription factor, is critical in maintaining viability of the metanephric blastema at this early stage of development.[21] With the invasion of the ureteric bud, the blastemal cells differentiate along distinct pathways. Cells adjacent to the ureteric bud tips condense and begin to display morphologic and molecular features characteristic of epithelial cells.

The molecular basis for nephron segmentation into various cell lines, such as podocytes, mesangium, or tubular lineages, is largely unknown. However, emerging evidence demonstrates a role for several gene families. The role of these genes is summarized below.

Several classes of genes are required for formation of podocytes and for directing the migration of endothelial cells into the glomerulus. As nephrogenesis proceeds, *Wt1* expression becomes restricted to the podocyte lineage. Transcription

of *Wt1* results in the formation of multiple isoforms generated by alternative splicing. Mutations in *Wt1* that prevent the generation of certain splice forms result in formation of abnormal glomeruli, implicating *Wt1* in glomerulogenesis.[22] *Lmx1b* is a transcription factor mutated in patients with nail-patella syndrome and is expressed in podocytes.[23] Mutational inactivation in mice decreases formation of foot processes and decreases expression of the α_3 and α_4 chains of type IV collagen. *Pod1* is a basic helix loop helix class transcription factor that is expressed in podocytes in S-shaped bodies. *Pod1* deficiency in mice results in arrested development at the single capillary loop stage of glomerular development.[24]

Kreisler (*MafB*), a leucine zipper class transcription factor is expressed in podocytes. *Kreisler* deficiency in mice results in failure of foot process attachment to the basement membrane.[25] The α_3 chain of α_3/β_1 integrin is required for formation of foot processes in mice.[26] Podocalyxin is a sulfated cell surface sialomucin that is expressed on the surface of podocytes. In a podocalyxin-deficient state, foot process and slit diaphram assembly is abrogated.[27] Recent studies suggest a central role for podocyte-derived vascular endothelial growth factor (VEGF)-A and Notch 2 in directing endothelial cell migration into glomeruli. Inactivation of VEGF-A in podocytes by genetic means in mice disrupts glomerular capillary formation.[28] Similarly, inactivation of *Notch2*, a member of a family of cell determination genes, results in a similar phenotype.[29]

Gene functions and renal dysplasia

The human and mouse genome projects have been complementary in generating a rapid expansion of our knowledge of human developmental biology. Yet, while the diversity of human phenotypes projects the existence of over 80 loci associated with renal dysplasia,[30] mutations in a much smaller number of genes have been identified so far. The functions of a subset of these genes have been elucidated in genetic mouse models, providing critical insights into the molecular control of normal and abnormal renal development.

Pax2

Heterozygous mutations in *Pax2* are found in patients with the renal coloboma syndrome (OMIM # 120330), which is characterized by renal hypoplasia and vesicoureteral reflux. Heterozygous *Pax2* mutations in mice results in a similar phenotype.[31] Investigation of *Pax2* suggests that it functions in the ureteric bud to promote cell proliferation and inhibit apoptosis.[32] These results support a model which proposes that *Pax2* controls the number of ureteric bud branches, thereby determining the number of nephrons formed.

Eya1

Eya1, a transcription factor, is mutated in patients with branchio-oto-renal (BOR) syndrome (OMIM # 113650) and unilateral or bilateral renal agenesis, or dysplasia.[33] In mice, the spatial pattern of *Eya1* expression overlaps that of *Gdnf* at the time of ureteric bud outgrowth. Since biallelic inactivation of *Eya1* causes renal agenesis and abrogates *Gdnf* expression,[6] *Eya1* is thought to function upstream of *Gdnf* to control ureteric bud outgrowth.

Sall1

Sall1, a transcription factor, is expressed in the metanephric mesenchyme at the time of induction by the ureteric bud. Mutations in *Sall1* exist in patients with Townes–Brock syndrome (OMIM # 107480). In *Sall1*-deficient mice, ureteric bud outgrowth occurs, but the bud fails to invade the metanephric blastema, resulting in renal agenesis. This failure of invasion appears to be due to a SALL1-dependent signal rather than the competency of the metanephric blastema to undergo induction.[34]

Gli3

The gene encoding Gli3 is mutated in patients with Pallister–Hall syndrome (OMIM # 146510) and renal dysplasia. GLI3 is one member among a family of GLI proteins that control gene transcription. Their actions are controlled by SHH. All *Gli3* mutations identified to date result in the expression of a truncated protein that functions as a transcriptional repressor. Recent investigations in mice provide insight into the biological significance of this mutant GLI3 isoform. GLI3 represses the transcription of GLI1 and GLI2, renal patterning genes including *Pax2* and *Sall1*, and genes that modulate the cell cycle (cyclin D1 and N-Myc).[35]

Glypican-3 and $p57^{KIP2}$

Investigation of the genes mutant in two human overgrowth syndromes, Simpson Golabi Behmel (OMIM # 312870) and Beckwith–Wiedemann (OMIM # 13650), is providing novel insights into the pathogenesis of medullary renal dysplasia. Patients with Simpson–Golabi–Behmel syndrome have mutations in Glypican-3, a glycosyl-phosphatidylinositol (GPI)-linked cell surface heparan sulfate proteoglycan. The pathogenesis of renal medullary dysplasia in *Gpc3*-deficient mice involves massive medullary collecting duct apoptosis preceded by increased ureteric bud proliferation.[36] Thus, *Gpc3* controls collecting duct cell number and survival. A role for control of the cell cycle in the pathogenesis of medullary renal dysplasia is further supported by the finding of medullary renal dysplasia in mice and humans (Beckwith–Wiedemann syndrome) with inactivating mutations in $p57^{KIP2}$, a cell cycle regulatory gene that encodes a cyclin-dependent kinase inhibitor.[37]

Table 1.1 lists clinical syndromes associated with known gene defects.[38–51]

Clinical aspects of maldevelopment syndromes

These advances in genetics have generated a revolution in our understanding of congenital malformations of the kidney. Although it has been accepted that there is an association among poorly developed kidneys, renal dysfunction, and

Table 1.1 Human gene mutations exhibiting defects in renal morphogenesis

Primary disease	Gene	Kidney phenotype	Reference
Alagille syndrome	*JAGGED1*	Cystic dysplasia	37
Apert syndrome	*FGFR2*	Hydronephrosis	38
Beckwith–Wiedemann syndrome	*p57^{KIP2}*	Medullary dysplasia	39
Branchio-oto-renal (BOR) syndrome	*EYA1*	Unilateral or bilateral agenesis/dysplasia, hypoplasia, collecting system anomalies	33
Campomelic dysplasia	*SOX9*	Dysplasia, hydronephrosis	40, 41
Fraser syndrome	*FRAS1*	Agenesis, dysplasia	42
Hyoparathyroidism, sensorineural deafness and renal anomalies (HDR) syndrome	*GATA3*	Dysplasia	43
Kallmann syndrome	*KAL1*	Agenesis	44
Mammary-ulnar syndrome	*TBX3*	Dysplasia	45
Renal coloboma syndrome	*PAX2*	Hypoplasia, vesicoureteral reflux	46
Renal cysts and diabetes syndrome	*HNF1β*	Dysplasia, hypoplasia	47
Simpson–Golabi–Behmel syndrome	*GPC3*	Medullary dysplasia	48
Townes–Brocks syndrome	*SALL1*	Hypoplasia, dysplasia, vesicoureteral reflux	49
Zellweger syndrome	*PEX1* (formerly *PAF1*)	Cystic dysplasia	50

urologic abnormalities, a generation ago it was widely held that some sort of obstructive process led to maldevelopment. The discovery of these genetic relationships has led to an understanding that maldevelopment results from failure of the programmed genetic control, with the likelihood that vesicoureteric reflux and urinary tract obstruction result from the same failure. As a result, we have come to understand that such disorders may demonstrate familial predisposition that can have clinical relevance.

The three categories of developmental abnormalities that can occur separately, or in concert, are renal hypoplasia, renal dysplasia, and abnormal development of the lower urinary tract.

Renal hypoplasia

Renal hypoplasia is characterized by a smaller than normal complement of nephrons in the kidney. The nephron structure and the overall renal architecture is well maintained. Hypoplasia can affect one or both kidneys. In renal hypoplasia, an abnormality in epithelial–mesenchymal interactions leads to decreased or abnormal branching of the ureter. Unless associated with other malformations, renal hypoplasia can be asymptomatic. Renal hypoplasia is often discovered as an incidental finding during an abdominal sonogram or other imaging studies, where a smaller than normal kidney is detected. Decreased renal function and chronic kidney disease (CKD) can be seen in severe cases with bilateral disease. Renal hypoplasia has been reported to be a predisposing condition for hypertension later in life.[1]

Multicystic Dysplasia

Multicystic dysplastic kidney (MCDK) is reported to be the second commonest renal anomaly diagnosed by prenatal ultrasound, with a reported prevalence of 1 in 3640 births.[52] MCKD can present as a flank mass in newborn infants. Renal ultrasound evaluation shows a large cystic non-reniform structure located in the renal fossa. The characteristic and diagnostic finding is absence of any function demonstrated by radionuclide scans. Vesicoureteric efflux in the contralateral normal kidney is the commonest associated urinary tract abnormality, and has been reported in approximately 25% of cases. [53] Hypertension can be seen in some patients, but appears to be less common than previously assumed.[53]

Wilms' tumor has been reported in patients with MCDK.[54] However, it has been argued that these cases of malignant degeneration in MCDK may have actually been nephrogenic rests.[53]

Gradual reduction in renal size and eventual resolution of the mass of the MCDK is common. At 2 years, an involution in

size by ultrasound has been noted in up to 60% of the affected kidneys.[55] Complete disappearance of the MCDK can occur in a minority of patients (3–4%) by the time of birth, and in 20–25% by 2 years.[53,55] Increase in the size of MCDK can be seen in some cases. The contralateral kidney shows compensatory hypertrophy by ultrasound evaluation.

Management of patients with MCDK has shifted from routine nephrectomy in the past, to observation and medical therapy. Because of the risk of associated anomalies in the contralateral kidney, VUR should be excluded. Renal ultrasound is generally recommended at an interval of 3 months for the first year of life and then every 6 months up to involution of the mass, or at least up to 5 years.[53] Compensatory hypertrophy of the contralateral kidney is expected and should be followed on ultrasound evaluations. Medical therapy is usually effective in treating hypertension in the small proportion of affected patients, but nephrectomy may be curative in resistant cases.

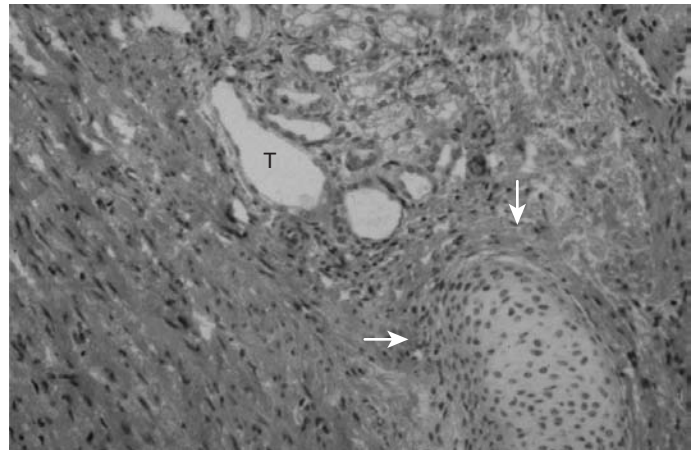

Figure 1.10 Microscopic section of a dysplastic kidney showing cartilage (arrows). Tubules (T) are poorly formed with cystic changes. (Photomicrograph courtesy of Arthur Cohen MD.)

Renal dysplasia

Renal dysplasia is characterized by the presence of malformed and rudimentary tissues (Figure 1.9) such as cartilage, or even calcified tissue (Figure 1.10) in the normal organ. Often, dysplasia is accompanied by hypoplasia of the kidney as well. Abnormalities of renal function and development of CKD should be expected in patients with severe bilateral renal dysplasia or those with additional urinary tract malformations, such as obstruction. Potter syndrome, characterized by oligohydramnios, pulmonary hypoplasia, renal failure, low set ears, and a beaked nose, may be observed in severe cases.

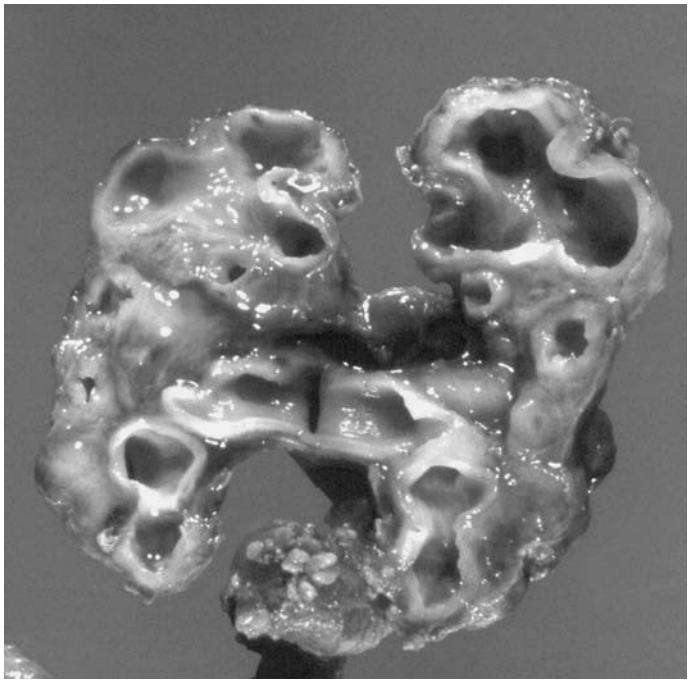

Figure 1.9 Cut section of a kidney with cystic dysplasia. Poorly defined renal architecture, lack of corticomedullary differentiation, and large cystic lesions are evident.

Concluding remarks

This chapter summarizes the major morphologic features of the developing and mature kidney. The concept of morphogenetic pathways is presented as a means of understanding how genes control cellular events that, in turn, build three-dimensional structures. Major genetic pathways that control normal renal branching morphogenesis and nephrogenesis are discussed. Genetic mutations associated with renal hypoplasia and dysplasia are presented. Advances in developmental genetics provide a means to understand the pathogenic significance of these mutations.

Acknowledgments

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2 Water and electrolyte handling by the kidney

Albert Quan, Raymond Quigley, Lisa M Satlin, and Michel Baum

The glomerulus produces an ultrafiltrate of plasma that essentially consists of a protein-free solution, identical to the composition of plasma. The adult kidney filters 150 L of fluid a day and delivers this fluid to the tubules where, under normal circumstances, 99% of this fluid is reabsorbed. The tubules selectively reabsorb the filtered solutes that are required by the organism, leaving waste products to be excreted in the urine. In addition to this filtration and reabsorption system, the kidney can also secrete many organic anions and cations via specific transporters to increase the efficiency of removal of some protein-bound solutes that are not filtered. A diagram of the nephron and the transporters involved in sodium and potassium reabsorption are shown in Figure 2.1.

Tubular solute transport

Proximal tubule

Reabsorption of sodium is the dominant task of the proximal tubule. The basic mechanism for sodium reabsorption, however, is similar in all segments of the nephron.[1] The sodium-transporting cells along the nephron have a basolateral Na^+/K^+-ATPase that generates a low intracellular sodium concentration (~10 mmol/L) and a significantly higher intracellular potassium concentration (~140 mmol/L) than the extracellular fluid. The Na^+/K^+-ATPase transports 3 sodium ions out of the cell in exchange for each 2 potassium ions it pumps into the tubular cell. This transport process is fueled by the energy source adenosine triphosphate (ATP). The ion composition gradient between the intracellular and extracellular compartments generated by the Na^+/K^+-ATPase and the basolateral potassium channel results in a negative potential difference of about –60 mV.

The low intracellular sodium concentration and the large negative potential difference provide a driving force for apical sodium entry into the cell. Most solute transport in the nephron is linked, either directly or indirectly, to the absorption of sodium. For example, glucose is reabsorbed from the luminal fluid by the proximal tubule via a sodium-dependent process. The energy required for glucose reabsorption is dependent on the low intracellular sodium and the negative potential difference generated by the Na^+/K^+-ATPase. Glucose is eventually transported from the tubular cell across the basolateral membrane via facilitated diffusion down its concentration gradient.

While the proximal tubule reabsorbs most of the sodium and water from the ultrafiltrate, it also reabsorbs all of the filtered glucose, amino acids, and required phosphate. While the proximal tubule is almost 10 mm long, most of the filtered bicarbonate, glucose, and amino acid absorption occurs in the first 2 mm of this segment (Figure 2.2).[2,3] The proximal tubule also reabsorbs 80% of the filtered bicarbonate and 60% of the filtered chloride.[2] The transepithelial potential difference in the early proximal tubule is lumen negative, which provides an electrical driving force for the paracellular reabsorption of chloride.[3]

The proximal tubule is the site for reabsorption of most of the filtered bicarbonate. Approximately two-thirds of bicarbonate is reabsorbed via a luminal Na^+/H^+ exchanger and one-third via a proton pump.[4,5] The secretion of a proton (H^+) through either of these two mechanisms results in the formation of carbonic acid (H_2CO_3), which dissociates into CO_2 and H_2O with the aid of carbonic anhydrase, which is present in the lumen. The CO_2 diffuses into the proximal tubule cell and reassociates with H_2O and, with the help of carbonic anhydrase in the cytoplasm of the proximal tubule, forms H_2CO_3. The H_2CO_3 dissociates back into a proton (H^+), which is again secreted across the apical membrane. The cellular bicarbonate is excreted across the basolateral membrane via an $Na(HCO_3)_3$ cotransporter.[6]

The preferential reabsorption of organic solutes and bicarbonate leaves the latter parts of the proximal tubule devoid of organic solutes and with a higher luminal chloride and lower luminal bicarbonate than that in the peritubular plasma.[1,3]

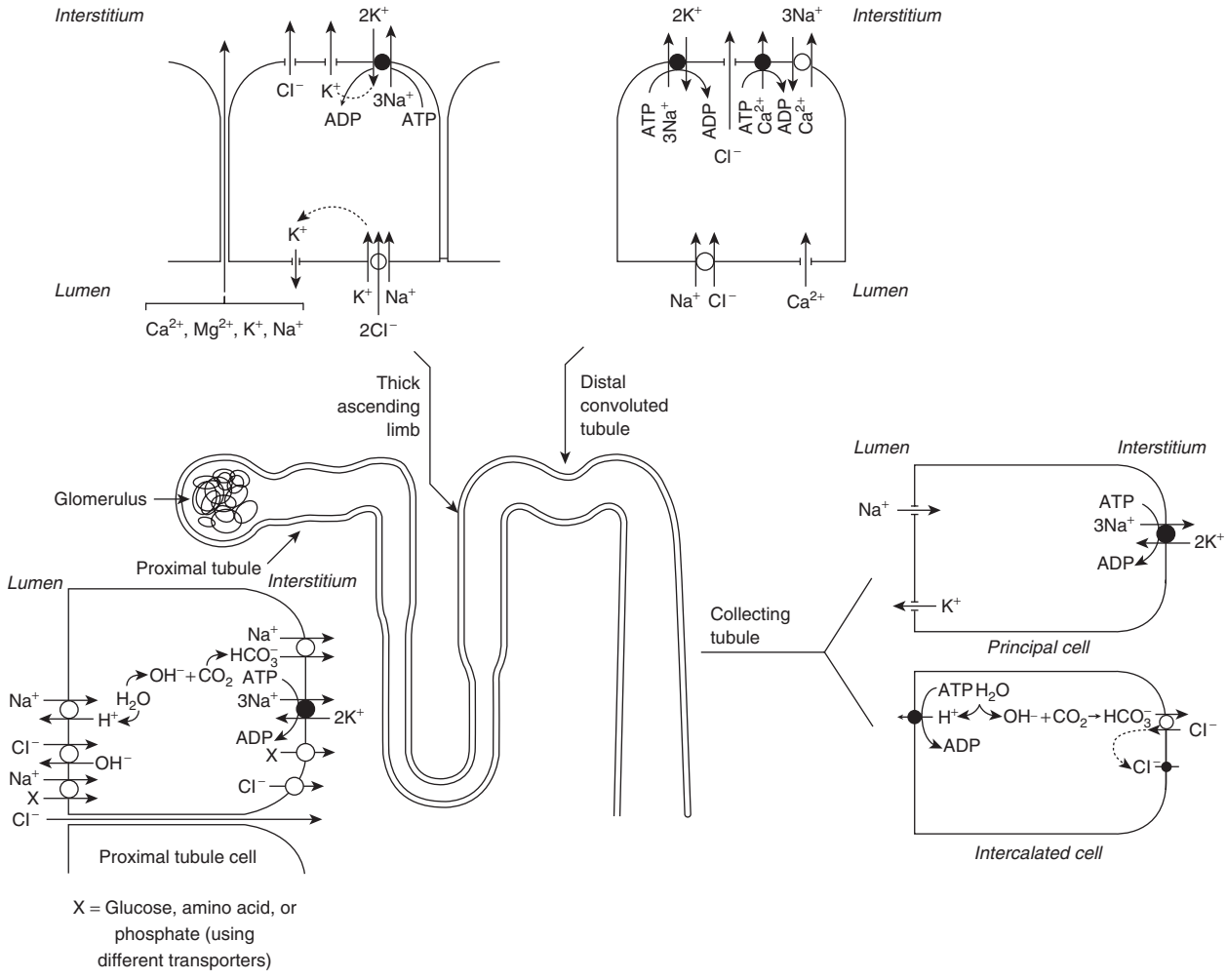

Figure 2.1 The nephron, showing the transporters present in each nephron segment responsible for NaCl transport.

Stated another way, the luminal fluid of the proximal tubule becomes almost isotonic normal saline in composition. This change in luminal fluid composition provides a gradient for bicarbonate to move from the peritubular plasma into the tubular lumen and chloride to move from the lumen into the peritubular plasma. Since chloride is far more permeable than bicarbonate, the movement of this anion generates a lumen positive potential that provides a driving force for sodium to move across the paracellular pathway into the peritubular plasma. Thus, the change in solute composition, which occurs in the early proximal tubule, generates a driving force for NaCl absorption without the additional expenditure of energy.

Approximately half of NaCl absorption is passive and paracellular.[7] The other half of NaCl transport is active and transcellular. It is mediated by the parallel operation of the Na^+/H^+ exchanger, which regulates bicarbonate reabsorption in the early proximal tubule, and a Cl^-/base exchanger that results in the net absorption of NaCl and secretion of proton and a base.[8] The nature of the base is unclear. There is evidence that it may be a hydroxyl ion, in which case one water molecule would be secreted for each NaCl absorbed.[1] There is also evidence that the base is a formate molecule, so that formic acid would be generated and reabsorbed (or recycled) back into the cell.[8]

Loop of Henle

The thin limbs of the loop of Henle also reabsorb NaCl without expending energy.[1] The thin descending limb is impermeable to NaCl, whereas it is highly permeable to water. Since the thin limb transverses the hypertonic medulla, water is abstracted and the luminal fluid becomes highly concentrated. At the bend of the loop, the permeability properties change drastically. The thin ascending limb becomes impermeable to water, while it is highly permeable to both urea and NaCl. Thus, the concentrated fluid that is progressing upwards into a less hypertonic environment has a gradient for NaCl and urea to diffuse out of the lumen into the medullary interstitium. This results in net NaCl absorption and helps generate a hypertonic medulla.

The thick ascending limb reabsorbs approximately 25% of the filtered NaCl.[1] Since this segment is impermeable to water, it is responsible for creating the 'primary effect' of generating a hypertonic medulla for urinary concentration and dilution. The

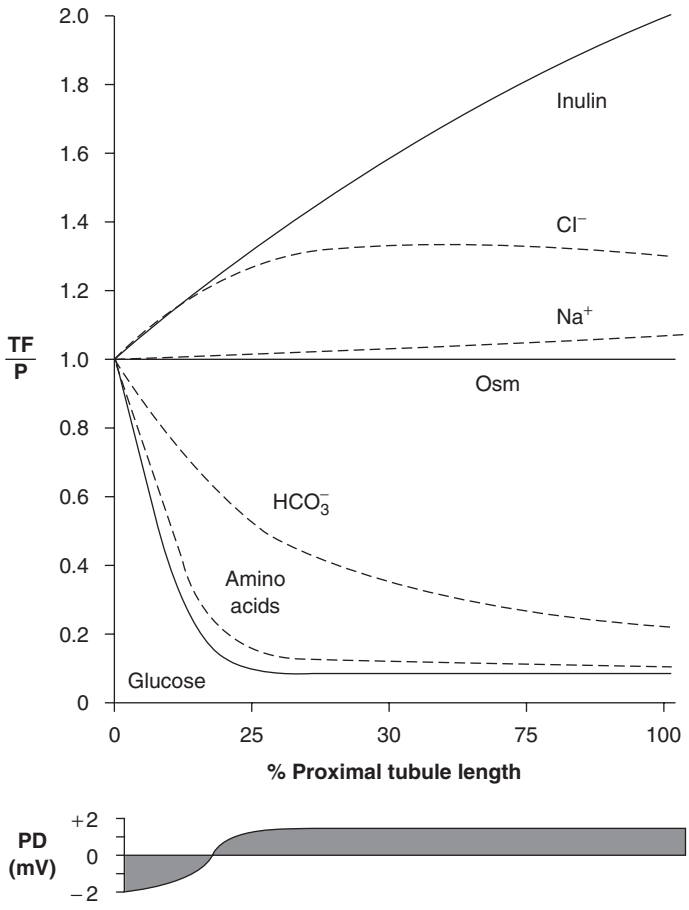

Figure 2.2 The changes that occur in solute composition along the proximal tubule (top). The early proximal tubule preferentially reabsorbs $NaHCO_3$ and organic solutes, delivering to the late proximal tubule a solution comparable to an isotonic NaCl. The bottom part of the figure shows the change in transepithelial potential, which initially is lumen-positive due to active sodium-dependent glucose and amino acid transport and then becomes lumen-negative due to passive paracellular chloride diffusion. (Reproduced with permission from Rector.[3])

apical membrane has a $Na^+/K^+/2Cl^-$ cotransporter that can be inhibited by furosemide and bumetanide. While this transporter results in the electroneutral absorption of sodium, potassium, and chloride, the lumen of this segment is positive due to the fact that there is an apical potassium channel and that some of the absorbed potassium recycles across the apical membrane into the lumen. This lumen positive potential is quite important since it generates the driving force for the paracellular absorption of magnesium and calcium in this segment. The paracellular pathway in this segment is unique in that it is very permeable to cations. Thus, administration of loop diuretics not only results in a decrease in NaCl absorption but also the enhanced excretion of magnesium and calcium as well as other cations. The sodium entering the thick ascending limb leaves via the Na^+/K^+-ATPase, while the chloride exits the basolateral membrane via either a KCl cotransporter or a chloride channel. Mutations in the $Na^+/K^+/2Cl^-$ (sodium–potassium–chloride) cotransporter, the apical K channel (rat outer medulla potassium; ROMK), or the basolateral CIC-KB (chloride) channel result in Bartter syndrome, an inherited disorder characterized by hypokalemic metabolic alkalosis, hyperreninism, and hyperaldosteronism.[9,10] The tubular defects present in Bartter syndrome mimic those induced by the administration of loop diuretics.

Distal tubule

The distal convoluted tubule is the segment that is responsible for the reabsorption of 5–10% of the filtered sodium.[1] Sodium is reabsorbed in this segment via a NaCl cotransporter, which is inhibited by thiazide diuretics. All cases of Gitelman syndrome are due to an inactivating mutation of this transporter.[11–13] Since the distal convoluted tubule is impermeable to water, the osmolality of the fluid that leaves this segment is 50 mOsm/kg water. This is the maximum dilution capacity of the human kidney. Thus, if there is no antidiuretic hormone (ADH) to increase the permeability of the collecting tubule to water, the final urine will have an osmolality of 50 mOsm/kg water.

In addition to the reabsorption of NaCl, the distal convoluted tubule also reabsorbs a substantial amount of calcium. Unlike the thick ascending limb, however, the reabsorption of calcium is transcellular. Inhibition of the NaCl cotransporter by thiazide diuretics results in an increase in calcium absorption by this segment. While loop diuretics cause an increase in urinary calcium excretion, thiazide diuretics decrease calcium excretion. This segment is also responsible for transcellular magnesium reabsorption. Thiazide diuretics result in urinary magnesium wasting.

Collecting duct

The collecting tubule is the final segment that adjusts the composition of the urine before excretion. While this segment reabsorbs only 1–3% of sodium, it nonetheless plays a critical role in regulating salt transport.[1] Sodium is reabsorbed by principal cells in this segment via an apical epithelial sodium channel (ENaC) (see Figure 2.1). This leaves the lumen with a negative potential difference as compared to the cell. This potential difference provides a driving force for potassium secretion, proton secretion, or the paracellular reabsorption of chloride. The sodium channel, potassium channel, the proton pump, and the basolateral Na^+/K^+-ATPase are all regulated by aldosterone. The sodium channel is inhibited by the diuretics amiloride and triamterene. These diuretics cause an increase in serum potassium since they decrease the lumen negative potential that augments potassium secretion. Finally, the distal part of the collecting tubule has urea transporters, which facilitate the absorption of urea and further increases the tonicity of the renal medulla.[14]

Concentration and dilution of urine

Whether the urine is concentrated or dilute compared with blood is dependent upon the presence or absence of ADH.

In the absence of ADH, the hypotonic urine formed in the thick ascending limb and distal convoluted tubule will be excreted with an osmolality of 50 mOsm/kg water. However, in the presence of ADH, water channels (designated aquaporin 2) are shuttled from the cytoplasm into the apical membrane.[15] This increases the permeability of the apical membrane for water. There are also water channels on the basolateral membrane designated aquaporin 3 and 4. The interstitium is quite hypertonic due to the accumulation of sodium, chloride, and urea via mechanisms discussed previously, and osmotic equilibration occurs. The urine of humans can be concentrated to an osmolality of 1200 mOsm/kg water. By comparison, desert rodents have very long loops of Henle and can concentrate their urine to over 3000 mOsm/kg water.

Antidiuretic hormone and water excretion

When the fluid reaches the thick ascending limb of Henle and early distal convoluted tubule, collectively known as the diluting segment, sodium and chloride is actively reabsorbed without water, so that the luminal fluid becomes hypotonic. This separation of salt and water is possible because these segments of the nephron have no water channels and have a low water permeability. The diluting segments are responsible for the generation of free water for excretion. If needed, the adult kidney can excrete ~30 L of free water a day. Thus, an adult with intact renal diluting capacity would have to drink over 30 L of water a day in order to develop hyponatremia. As discussed below, this is not true in case of the neonate.

The cortical and medullary collecting tubules can alter their water permeability in response to the absence or presence of ADH, and modify the concentration (osmolality) of the final urine.[15] As seen in Figure 2.3, as ADH binds to the basolateral receptor (V2 receptor or V2R), it stimulates the production of cyclic adenosine monophosphate (cAMP). This, in turn, leads to intracellular signals that trigger the insertion of vesicles containing aquaporin 2 (AQP2), a water channel, into the apical membrane. The water channels allow for the rapid transport of water into the collecting duct cell, which subsequently exits passively into the hypertonic medulla along the basolateral membrane through two other water channels, aquaporin 3 (AQP3) and aquaporin 4 (AQP4). This reabsorption of water leads to a final urine that, in adults, is concentrated to values as high as 1200 mOsm/kg water.

The production of maximally concentrated urine also requires the maintenance of the medullary osmotic gradient and the pituitary release of ADH. In the absence of ADH, the AQP2-containing vesicles remain in the cytoplasm of the collecting duct cells and the apical membrane water permeability remains low. This prevents reabsorption of water from the tubular lumen and the final urine is allowed to remain dilute. This mechanism of insertion and removal of the AQP2 water channels from the apical membrane allows for fine regulation of the final urine osmolality in response to ADH.

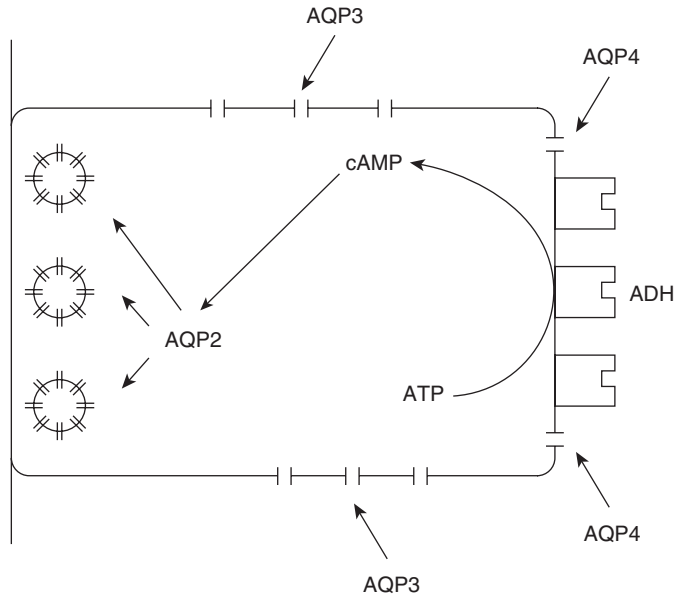

Figure 2.3 Collecting duct cell showing interactions of antidiuretic hormone (ADH) and aquaporins (AQP2, AQP3 and AQP4) in the process of water reabsorption. The collecting duct principal cell contains AQP2 in vesicles that can be inserted into the apical membrane in response to ADH. AQP3 and AQP4 are present in the basolateral membrane, so that the water can be transported into the bloodstream. A defect in the pathway for ADH response will lead to nephrogenic diabetes insipidus and predispose the patient to hypernatremia.

The secretion of ADH is regulated by the plasma osmolality and intravascular volume. Small increases in serum osmolality stimulates the secretion of ADH. Significant intravascular volume loss is a potent stimulus for ADH secretion that can override its regulation by the serum osmolality. This can contribute to the development of hyponatremia.

Regulation of serum sodium

The kidney regulates the serum sodium concentration within a narrow range, primarily by regulating free water excretion. Thus, the primary mechanism that defends the body from hyponatremia is the kidney's capacity to excrete free water. Disorders that limit the kidney's ability to excrete adequate amounts of free water can lead to hyponatremia. Although the kidney can retain much of the filtered free water to defend against hypernatremia, the primary defense against the development of hypernatremia is thirst. Hypernatremia is usually seen under circumstances of inadequate access to free water, or if a defect in the central nervous system that impairs the normal thirst response is present.

Regulation of tubular sodium transport

Proximal tubule

The proximal tubule reabsorbs 60% of filtered sodium and chloride and is a major site of nephron sodium regulation.[1] Proximal tubular transport is modulated, in part, by peritubular capillary physical factors such as the peritubular capillary hydrostatic pressure and oncotic pressure.[16] The peritubular capillary hydrostatic pressure opposes net proximal tubular sodium reabsorption, whereas the peritubular capillary oncotic pressure promotes proximal tubular sodium reabsorption. Therefore, following volume expansion, the peritubular capillary protein concentration falls, while the hydrostatic pressure rises, both of which reduce proximal tubular sodium reabsorption. With volume contraction, however, peritubular capillary protein concentration rises and peritubular capillary hydrostatic pressure falls, both of which increase tubular sodium reabsorption.

The systemic renin–angiotensin system plays an important role in the regulation of proximal tubule sodium reabsorption. Circulating angiotensin II has been shown to directly stimulate proximal sodium reabsorption. These stimulatory effects of angiotensin II occur in the absence of changes in the glomerular filtration rate. In addition to the systemic renin–angiotensin system, the proximal tubule contains all of the components of an autonomously functioning intrarenal renin–angiotensin system and secretes angiotensin II into the lumen at concentrations 100-fold higher than that found in the plasma. Both the systemic and intraluminal angiotensin II stimulate proximal tubular sodium transport.[17]

Sympathetic renal nerves innervate the proximal tubule and regulate sodium homeostasis. During volume contraction, renal nerve activity increases and stimulates proximal tubule sodium transport. Conversely, renal nerve activity decreases during volume expansion and subsequently decreases transport. The renal nerves also increase renin secretion and thus contribute to systemic angiotensin II activity.

Loop of Henle

The loop of Henle reabsorbs approximately 25–30% of sodium from the glomerular ultrafiltrate which can be stimulated by both ADH and sympathetic nerve activity.[1] The importance of the thick ascending limb to sodium reabsorption is highlighted in patients with Bartter syndrome, where defects in either the apical membrane ROMK channel, $Na^+/K^+/2Cl^-$ transporter, or the basolateral CIC-KB channel all lead to extracellular volume contraction with hypokalemic metabolic alkalosis. Whereas prostaglandin E (PGE_2) has no direct effect in this segment, PGE_2 inhibits the ADH-induced increases in sodium reabsorption.

Distal tubule

Both circulating and luminal angiotensin II increase distal tubule sodium reabsorption. The renal nerve also innervates the distal tubule and augments sodium reabsorption. Sodium reabsorption in the distal tubule is also load dependent. The importance of the NaCl cotransporter is illustrated in patients with Gitelman syndrome, where a defective NaCl cotransporter leads to extracellular volume contraction, salt wasting, and metabolic alkalosis.

Cortical collecting duct

Only 1–3% of sodium reabsorption occurs in the collecting duct, but this segment is responsible for the final modulation of sodium absorption, and thus plays a critical role in the regulation of extracellular fluid volume.[1] Sodium absorption in this segment is primarily regulated by aldosterone, which increases the number of ENaC channels on the apical membrane and raises the apical sodium permeability. Activity of the basolateral Na/K-ATPase pump is also increased by aldosterone, which serves to lower intracellular sodium, providing a greater driving force for tubular sodium reabsorption. ADH also increases the apical sodium transport, promoting insertion of ENaC in the apical membrane.

Solute and water transport in the neonatal kidney

The glomerular filtration rate (GFR) of an adult kidney is ~100 ml/min. The term newborn has a GFR of 2 ml/min. Even after correction for body surface area, the neonate's GFR is only 30 ml/min/1.73 m^2. Premature neonates have an even lower value, but the extrauterine maturational increase in GFR occurs at the same rate as if the baby was still in the womb.[18,19] The GFR increases to adult values, corrected for surface area, by 6–12 months of age.

The most important difference between the neonate and the adult kidney is that the adult kidney functions to maintain a constant composition and volume of the extracellular fluid. The intake of salt and water is matched by the urinary excretion, and both fluid overload and volume depletion are avoided. The neonate, on the other hand, must maintain a slightly positive balance for all electrolytes to allow for growth.

The driving force for most active solute transport is the low intracellular sodium concentration and the negative cell potential difference. The Na^+/K^+-ATPase pump generates this low intracellular sodium and potential difference but, as can be seen in Figure 2.4, the activity of the pump is less in each nephron segment in neonates compared with adults.[20] The lower activity of the pump parallels lower solute transport in each nephron segment in the neonate compared with the adult.

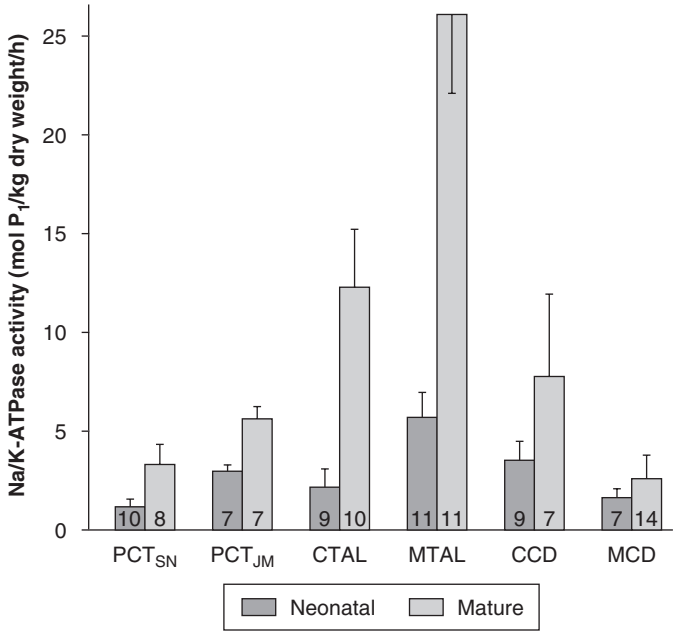

Figure 2.4 Na/K-ATPase activity in neonatal and adult nephron segments. In every segment there is a maturational increase: superficial proximal convoluted tubule (PCT_{SN}), juxtamedullary proximal convoluted tubule (PCT_{JM}), cortical thick ascending limb (CTAL), medullary thick ascending limb (MTAL), cortical collecting duct (CCD), and medullary collecting duct (MCD).

The maturation of the neonatal proximal tubule keeps pace with the developmental increase in GFR, also known as the glomerulotubular balance. The neonatal proximal tubule reabsorbs all of the filtered glucose, amino acids, and most of the filtered bicarbonate. Some significant differences, however, need to be noted. First, while glomerulotubular balance is maintained in term neonates, this is not true of premature neonates born before 34 weeks of gestation. The proximal tubules of these infants cannot keep pace with the glomerular filtrate delivered and thus have an apparent Fanconi syndrome with glucosuria, amino aciduria, and renal tubular acidosis.[18] Although the rate of all transporters studied is less in the neonate than in the adult, there is one important exception. The rate of phosphate transport is higher in the neonatal proximal tubule, which contributes, in part, to the serum phosphate being higher in the neonate than in the adult.[21–23] In addition, an isoform of the apical sodium–phosphate cotransporter in the neonatal proximal tubule is responsible for a large fraction of transport in the neonate, which plays only a minor role in the adult nephron.[24] In addition to quantitative differences in tubular transport, there is now firm evidence for mechanistic differences between the neonatal and adult nephron. Whereas the rates of all of the transporters, including the Na^+/H^+ exchanger and $Na(HCO_3)_3$ cotransporter, are less in neonates,[25] there does not appear to be any H^+-ATPase activity in the neonate,[5] which accounts for one-third of proton secretion in the adult proximal tubular segment.[4,5]

NaCl transport from the proximal tubular lumen to the blood occurs via both transcellular and paracellular mechanisms. Whereas chloride permeability is high in the adult proximal tubular segment, it is almost nonexistent in the neonate, and thus there is no passive chloride transport.[26,27] Finally, water transport deserves a mention, as well. Aquaporin 1 is less abundant in the neonate than in the adult proximal tubular segment but the permeability of water is actually higher in the neonate.[28] This is because the neonatal proximal tubule cytoplasm offers less resistance to water flow than that of the adult segment.

The maturation of the remainder of the nephron functions parallels the maturation of the Na^+/K^+-ATPase. Thus, the $Na^+/K^+/2Cl^-$ in the thick ascending limb is less mature than that of the adult.[29] Special mention needs to be made of the transporters in the collecting tubule, since these have significant clinical relevance. The neonatal cortical collecting duct essentially has no apical Na^+ channel and K^+ channel activity.[30,31] The maturational increase in apical Na^+ channel occurs well before that of the K^+ channel.[32,33] This paucity of K^+ channel occurs despite the fact that there are adequate aldosterone and aldosterone receptors. The lack of K^+ channels limits the ability of neonates to excrete potassium and can predispose them to hyperkalemia.

An increase in glomerular filtration rate in the developing infant results from a number of factors. By far, the most important factor responsible for the maturational increase in GFR is the increase in glomerular capillary surface area, followed by the developmental increase in ultrafiltration pressure, while there is only a small increase in hydraulic permeability.[34]

The renal tubules must keep pace with the maturational increase in GFR. What causes the maturational increase in transport? The best-studied transporter is the Na^+/H^+ exchanger (NHE-3) in the proximal tubule. There is substantive evidence that the postnatal increase in glucocorticoids is the main factor that results in the maturational increase in this transporter. Administration of glucocorticoids to late gestation fetuses results in a maturational increase in Na^+/H^+ antiporter activity, NHE-3 protein and mRNA abundance, and bicarbonate absorption to levels comparable to that of adults.[35,36] Prevention of the maturational increase in glucocorticoids by neonatal adrenalectomy, by and large, prevents the maturational changes in these parameters.[37] There remains a small increase in Na^+/H^+ antiporter activity and NHE-3 protein and mRNA abundance in the absence of glucocorticoids, so that other factors must also play a minor role.

Finally, one must compare salt handling and the response to a volume load in neonates and adults. If one compares the effect of an isotonic volume challenge in a neonate to a comparable volume challenge in an adult, one finds that the adult is able to excrete the salt load far more briskly than the neonate.[38] This is important clinically, as neonates are able to be in positive salt

balance despite drinking a fluid, mother's milk, which has a very low salt content. It remains unclear how this occurs, but there is evidence that there is augmented sodium absorption in the distal convoluted tubule in the neonatal kidney in response to an isotonic fluid load compared with that of an adult.[39] In addition, the renin–angiotensin system probably plays a role in the difference in the ability to excrete a salt load between neonates and adults, since losartan increases the rate of natriuresis and diuresis in response to a volume load in neonates.[40] While the term neonate is adept at retaining NaCl, the premature neonate has problems with renal salt wasting due to the immaturity of the transporters in the kidney. This results clinically in hyponatremia and volume depletion unless these infants have salt supplementation.

CLINICAL DISORDERS

Hyponatremia

Definition

Hyponatremia is defined as a serum sodium concentration of less than 136 mmol/L.[41] True hyponatremia must be distinguished from pseudohyponatremia (or factitious hyponatremia), which may result either from the serum sodium assay technique or from hyperglycemia. The measured serum sodium concentration may also be spuriously low if the blood is hyperlipidemic or hyperproteinemic, and the flame photometry method is used for electrolyte assay. However, most modern laboratories use ion-selective electrodes for electrolyte assay, which eliminates this type of an error. Hyperglycemia can also result in hyponatremia by the osmotic action of glucose, which facilitates shift of water from the intracellular compartment into the intravascular compartment. This leads to dilution of the serum sodium and resultant hyponatremia. In general, for each 100 mg/dl rise of glucose in the serum, the sodium will be lowered by 1.7 mEq/L (1.7 mmol/L). In contrast to the patient with true hyponatremia, these patients are not hypotonic.

Etiology

Hyponatremia is an electrolyte disturbance that is encountered commonly in sick children. In one study, hyponatremia was diagnosed in 131 of the 1586 (8.2%) patients seen in the emergency room in whom at least one determination of serum sodium was performed.[42] In the same study, 40 of the 432 hospitalized children (9%) in whom at least two serum sodium estimations were available developed hyponatremia during hospitalization.

In order to excrete free water, an adequate delivery of fluid to the diluting segment is necessary, the diluting segment must be functional, and ADH secretion must be suppressed. Disturbance in one or more of these three steps results in the inability to excrete free water and predisposes to the development of hyponatremia. The clinical conditions that interfere with these processes and lead to hyponatremia are outlined in Table 2.1.

Clinical manifestations

Early manifestations of hyponatremia are nonspecific and consist of anorexia, nausea, vomiting, and muscle cramps. Children may describe these symptoms as 'not feeling well'. More advanced hyponatremia leads to lethargy, agitation, and disorientation. Seizures can occur in rapidly evolving hyponatremia (in 48 hours), especially if the serum sodium level declines below 125 mmol/L.

Table 2.1 Causes of hyponatremia

Low effective arteriolar volume	Normal effective arteriolar volume
With low total body water	• SIADH
GI losses:	• Hypothyroidism
• Diarrhea	• Adrenal insufficiency
• Vomiting	• Water intoxication
Renal losses:	• Renal failure
• Congenital adrenal hyperplasia	
• Bartter syndrome	
• Gitelman syndrome	
• Diuretics	
• Salt wasting renal diseases	
• Cerebral salt wasting	
Other losses:	
• Cystic fibrosis	
With high total body water (edema)	
• Nephrotic syndrome	
• Cirrhosis	
• Congestive heart failure	

Diagnostic evaluation

As shown in Table 2.1, it is helpful to organize the differential diagnosis of hyponatremia based on the volume status of the patient. Total body water is approximately 60% of body weight. About two-thirds of this water is distributed in the intracellular compartment and one-third in the extracellular fluid compartment. The extracellular compartment is further

divided into the plasma volume and the interstitial fluid. It should be emphasized that the kidney and volume sensors in the cardiovascular system respond to the circulating plasma volume, which is also termed the 'effective arteriolar volume'. This conceptual body fluid compartment may not correlate with the measured plasma volume. It is best thought of as the extent of fullness of the intravascular compartment, which is dependent on the volume of that compartment and the cardiac output. In congestive heart failure, for example, the plasma volume is usually expanded, but the effective arteriolar volume is low because of the low cardiac output. Similarly, in nephrotic syndrome the total body water may be elevated, but because of the low plasma oncotic pressure, most of the fluid is in the interstitial space and the effective intravascular volume is low.

The most common cause for the inability to excrete free water is intravascular volume depletion. This is usually associated with total body volume depletion, but, as shown in Table 2.1, it can be found in patients with edema who may also have a decreased effective arteriolar volume, such as in congestive heart failure, cirrhosis, and nephrotic syndrome. During effective arteriolar volume contraction, the GFR decreases and the proximal tubule responds to volume contraction by reabsorbing a larger fraction of the filtered load of sodium and water. This greatly diminishes the distal delivery of fluid, and thus decreases the amount of free water that can be excreted. In addition to the decreased distal delivery of fluid to the diluting segment, volume depletion also enhances ADH secretion. Thus, the combination of decreased distal fluid delivery to the diluting segment and high ADH levels results in the inability to excrete free water, leading to the development of hyponatremia.

Patients treated with diuretics develop hyponatremia through multiple mechanisms. Diuretics lead to volume depletion, activating the mechanism described above. In addition, they interfere with the ability of the diluting segment (thick ascending limb and distal convoluted tubule) to transport sodium from the tubular lumen to the blood and generate free water.

Newborn infants are especially predisposed to hyponatremia because of their low GFR and low delivery of fluid to the distal diluting segment. Feeding of inappropriately dilute formula can result in intake of excessive amounts of hypotonic fluid, which may exceed the renal capacity to excrete the free water, resulting in hyponatremia. This can occur despite an intact diluting system and achieving a urine osmolality of 50 mOsm/L.

Syndrome of inappropriate secretion of ADH

Inappropriately elevated circulating levels of the antidiuretic hormone can lead to a distinct disorder associated with hyponatremia, which is termed the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). A number of clinical conditions, such as pain, pulmonary disorders, increased intracranial pressure, various malignancies, and drugs, can result in SIADH. Carbamazepine, cyclophosphamide, vincristine, chlorpropamide, narcotics, antipsychotics, antidepressants, and nonsteroidal anti-inflammatory agents are the drugs most commonly associated with SIADH.

Pathophysiology of SIADH

The pathophysiology of hyponatremia in SIADH is related to enhanced collecting duct water permeability due to ADH, resultant reabsorption of free water, and development of hyponatremia. Under these circumstances, urine is concentrated in the face of hyponatremia and hypo-osmolality. Although the urine osmolality can decrease to near isotonic levels over time, the urine remains inappropriately concentrated for the degree of hypo-osmolality. The mechanisms responsible for the decrease in urine osmolality are complex, and probably involve washout of the medullary concentration gradient and the effects of atrial natriuretic factor (ANF). These homeostatic mechanisms are an attempt to prevent the uncontrolled increase in body water. Although clinically detectable edema is uncommon in SIADH, the patient's weight is often increased. The volume status of these patients is usually normal, or slightly increased. As a result, their blood urea nitrogen (BUN) and serum uric acid concentrations are usually low and the urine sodium concentration (a reflection of the increased effective arteriolar volume status) is usually high. The diagnosis of SIADH should be considered in patients with hyponatremia, no obvious edema, and inappropriately concentrated urine, increased urinary excretion of sodium, and low serum uric acid level.

The mainstay of treatment for SIADH is fluid restriction and treatment of the underlying cause. In some cases, SIADH may become a chronic condition. In these circumstances, treatment with an agent to disrupt the action of ADH may be necessary. These agents include demeclocycline and lithium. Demeclocycline is preferred, since it is less toxic. In the future, non-peptide antagonists to ADH may become useful clinical tools for treatment of patients with SIADH.

Management of hyponatremia

The treatment of hyponatremia depends on the specific cause of hyponatremia. The recommendation to give sodium versus fluid restriction will hinge primarily upon the volume status of the patient. If the patient has volume depletion from gastrointestinal or other losses, the volume deficit must be replaced to replenish the patient's extracellular fluid volume. After appropriate volume expansion, the patient will be able to regulate free water excretion to correct the serum sodium concentration. Patients with SIADH as the cause of hyponatremia need to be fluid-restricted. In general, giving patients with SIADH extra sodium to correct their serum sodium will not be helpful and many times can exacerbate the hyponatremia. Other patients with excess fluid or edematous states, such as in congestive heart failure or nephrotic syndrome, will also need

to be fluid restricted. Administering sodium to these patients will worsen their edema.

For purposes of correction, the sodium deficit is calculated using the following equation:

$$\text{Na deficit} = [Na_{Desired} - Na_{Observed}] \times [(\text{Weight in kg}) \times (0.6\ \text{L/kg})]$$

where $Na_{Desired}$ is the serum sodium value you want to correct to and $Na_{Observed}$ is the actual measured sodium. The serum sodium should never be corrected faster than 15 mmol/L/24 h because of the risk of developing central pontine myelinolysis. Thus, if the patient has a serum sodium concentration less than 125 mmol/L, the correction of the sodium should take more than 24 hours. If the patient is symptomatic (i.e. has neurological symptoms such as seizure), the sodium may need to be increased more rapidly but once the serum sodium has reached 125 mmol/L the seizure activity usually subsides. After the seizure abates, the sodium should be increased slowly as described above.

Clinical case

An 8-year-old, 25 kg boy was admitted to the hospital with meningitis. After appropriate cultures were sent, he was started on intravenous antibiotic therapy as well as intravenous fluids – D5 1/2NS (half normal saline) at 65 ml/h. The next morning, his serum sodium was found to be 125 mmol/L and creatinine was 0.7 mg/dl. His serum glucose was 100 mg/dl and his serum osmolality was found to be low, at 260 mOsm/kg water, while his urine osmolality was 510 mOsm/kg water. Thus, he had true hyponatremia and not pseudohyponatremia. As seen in Table 2.1 and discussed above, the first step to narrow the differential diagnosis is to determine his volume status. On physical examination, he was found to have a heart rate of 90 beats/min and a blood pressure of 116/68 mmHg. His skin turgor was good and he had moist mucous membranes. To help with the volume assessment, the boy's BUN and uric acid were measured as well as his fractional excretion of sodium (FENa). His BUN was 8 mg/dl and uric acid was 1.2 mg/dl. His FENa was found to be 2%. Additional laboratory values include normal serum creatinine.

Comment

This patient was found to have a number of indicators pointing to an increased extracellular fluid volume: BUN and uric acid were low, FENa was high, and vital signs and physical examination did not indicate volume depletion. With the urine osmolality being clearly elevated in a patient with normal renal function and low serum osmolality, this patient had SIADH. The treatment of hyponatremia in this case would be to fluid restrict the patient. The degree of restriction will be dictated by how quickly the sodium corrects. It is generally best to restrict to insensible water loss (about one-fourth of the maintenance fluid rate) and then increase or decrease the fluid intake depending on the response of the serum sodium.

Hypernatremia

Definition

A serum sodium level greater than 147 mmol/L qualifies for the diagnosis of hypernatremia. Clinically significant manifestations, however, rarely arise below a serum sodium concentration of 150 mmol/L.

Etiology

Hypernatremia is a less common disorder seen in children in the temperate climates. The prevalence of hypernatremia, depending on the type of data used, has been estimated to be 0.22–1.4% of hospitalized children.[43] Although the kidney can concentrate the urine to retain free water, the body's primary defense against hypernatremia is an adequate thirst mechanism and replenishing free water.[44] As the serum sodium concentration (and therefore the serum osmolality) increases, the thirst center in the hypothalamus is stimulated and the individual drinks fluids in order to normalize the serum osmolality. Restriction or inability to access free water can lead to hypernatremia.

The concentrating ability of the kidney is dependent on three factors:

1. the ability of the hypothalamus and pituitary to synthesize and secrete ADH
2. generation and maintenance of an osmotic gradient across the collecting duct
3. the response of the collecting duct to ADH to increase water permeability, as shown in Figure 2.4.

Thus, the inability to maximally concentrate the urine may be due to a defect in one or more of these factors.

Gastroenteritis, leading to a relatively greater loss of water in comparison to sodium, is a common etiology of hypernatremia in infants. Accidental excessive salt intake (salt poisoning) has been reported to cause hypernatremia in infants and small children. Table 2.2 lists the causes of hypernatremia in children.

Diagnostic evaluation

In evaluating a patient with hypernatremia, one must determine if the thirst mechanism is intact. Ability of the patient to access water should be looked into, especially in those who are unable to care for themselves. Gastrointestinal loss of hypotoxic fluid from diarrhea is a cause of hypernatremia in children Inability to concentrate urine in renal diseases such as renal dysplasia, obstructive uropathy, or diseases of the interstitium can

Table 2.2 Causes of hypernatremia

Net water deficit	Net sodium gain
Restriction of access to water	**Therapy-related**
Impaired thirst mechanism	Hypertonic saline use
	Hypertonic sodium bicarbonate use
	Hyperalimentation
Renal water loss:	**Intentional or accidental salt poisoning**
Central diabetes insipidus:	
Brain injury	
Meningitis	
Suprasellar tumors	
Histiocytosis	
Granulomas (sarcoidosis, tuberculosis)	
Nephrogenic diabetes insipidus:	
Renal dysplasia	
Obstructive uropathies	
Postobstructive diuresis	
Interstitial diseases	
Sickle cell disease	
Hypokalemic nephropathy	
Hypercalcemic nephropathy	
Drugs – osmotic diuretics, lithium, amphotericin B, gentamicin, vinblastine, demeclocycline, colchicine	
GI loss	
Diarrhea	
Burn injury	

result in excessive free water loss and hypernatremia. Most of these patients are, however, able to maintain their serum sodium concentration and osmolality in a normal range, as long as they are able to drink water and replace the urinary loss of free water. Hypernatremia can result iatrogenically with intravenous use of hypertonic saline or sodium bicarbonate, especially in neonates and young infants. Accidental and intentional 'salt poisoning' is uncommon, but this may need to be considered under appropriate circumstances in an infant or a young child.

Clinical manifestations

The clinical manifestations of hypernatremia in early stages can be non-specific, such as irritability, fever, muscle twitching, and increased muscle tone. These symptoms give way to nuchal rigidity, lethargy, and seizures. Many patients may be suspected of having meningitis. Coma may occur in severe hypernatremia. Intracranial bleeding in severe cases of hypernatremia may be associated with additional focal or generalized neurological findings. Intravascular volume is better preserved in hypernatremic dehydration as compared to isonatremic dehydration, and the classic signs of hypovolemia may be masked until severe volume depletion has occurred. Reversible hyperglycemia and hypocalcemia are commonly present in untreated hypernatremia.

Diabetes insipidus

Diabetes insipidus (DI) is characterized by the inability of the patient to concentrate urine. This can be a result of a defect in the secretion of ADH (central diabetes insipidus) or the inability of the kidney to respond to ADH (nephrogenic diabetes insipidus). Clinical manifestations of DI consist of polyuria and polydypsia. As noted above, many of these patients are able to maintain their serum sodium and osmolality in a normal range by drinking the required volume of water.

Central diabetes insipidus usually results from an inability to secrete ADH from the posterior pituitary. Tumors in the hypophyseal region (craniopharyngioma, glioma), accidental trauma to the pituitary, or neurosurgical procedures can lead to interruption of ADH secretion and DI. Some patients with holoprosencephaly have defects in the secretion of ADH. Central diabetes insipidus can also be seen with global dysfunction of the pituitary, or panhypopituitary syndrome. The treatment of central diabetes insipidus is to replace ADH, usually in with DDAVP (desmopressin).

Nephrogenic diabetes insipidus results from a defect in the collecting duct that prevents the normal response to ADH. Nephrogenic diabetes insipidus can be congenital or acquired. The most common inherited defect is due to a mutation in the ADH receptor (V2R), which is located on the X chromosome. Patients with this mutation are males who present with repeated bouts of dehydration and fever due to the urinary loss of free water. Inherited defects in the AQP2 water channel have also been recently described. Most of these defects are inherited in the autosomal recessive fashion, but there have been mutations with autosomal dominant transmission.

Nephrogenic diabetes insipidus can also result as an acquired lesion. Obstructive uropathy can damage the cortical collecting duct so that ADH is ineffective. Drugs such as lithium, amphotericin, and demeclocycline can also impair the action of ADH on the collecting duct. Long-standing hypokalemia and hypercalcemia can also cause acquired DI.

A water deprivation test can determine whether a patient has diabetes insipidus and whether it is central or nephrogenic. Water is withheld for a period of time until either the urine osmolality increases significantly or there is a rise in the serum sodium concentration with no change in the urine osmolality. If the urine osmolality increases significantly, the patient has primary polydipsia. If the patient's serum sodium increases and the urine osmolality remains hypotonic, the patient has diabetes insipidus. To determine if this is due to a central or renal defect, ADH is administered. An increase in the urine

osmolality with ADH indicates that the patient has central diabetes insipidus. It should be pointed out that patients who present with hypernatremia have already been water-deprived. At presentation, one should always measure the urinary osmolality to determine if the patient has a urinary concentrating defect. This will obviate the need to perform the water deprivation test in the future.

Management of hypernatremia

The principal treatment of hypernatremia is to provide enough free water to correct the elevation in serum sodium concentration. The amount of water needed is known as the 'free water deficit' and is calculated by the following equation:

$$\text{Free water deficit} = \left[\frac{Na_{Observed} - Na_{Desired}}{Na_{Desired}}\right] \times [(Weight\ in\ kg) \times (0.6\ L/kg)]$$

where $Na_{Desired}$ is the serum sodium value you want to achieve and $Na_{Observed}$ is the actual measured sodium. The free water deficit is calculated in liters, and needs to be converted to milliliters for use in a small child or an infant.

The serum sodium should not be corrected by more than 15mmol/L/day. Lowering the serum sodium (and therefore osmolality) too quickly can result in cerebral edema, which causes neurological manifestations, including coma and death. The pathogenesis of cerebral edema is believed to be due to the development of osmotically active 'idiogenic' osmoles within the brain cells. These 'idiogenic' osmoles maintain a hypertonic intracellular environment and permit movement of water from the extracellular compartment into the brain cells when hyponatremia is corrected rapidly, resulting in cell swelling and brain edema.

One of the difficulties in treating hypernatremic dehydration is to determine if the patient has an extracellular fluid volume deficit. Patients with hypernatremic dehydration can appear more volume replete than they actually are. In face of intravascular volume depletion, these patients may need to receive an isotonic fluid bolus prior to receiving the free water replacement. Once the intravascular volume is expanded, the kidney will be able to excrete the excess sodium. Again, this needs to be done carefully so that the patient's serum sodium does not decrease too rapidly and so that the patient does not become fluid overloaded.

Fluid balance

Renal response to volume depletion

Maintenance of normal extracellular fluid volume is essential for optimal cardiovascular function. The extracellular fluid is primarily composed of sodium and chloride ions, thereby making the homeostasis of the extracellular fluid compartment dependent and closely related to the homeostasis of sodium.[45] Extracellular fluid volume is regulated within a narrow range, despite variations in dietary sodium intake and sodium losses. Daily sodium intake can range from 10 mmol/day (250 mg/day) to over 1000 mmol/day (over 20 g/day). The kidneys regulate sodium reabsorption and excretion in the face of these fluctuations in sodium intake and losses, and defend against changes in the extracellular fluid volume. As discussed in the foregoing section, the *modus operandi* of renal sodium regulation rests with modulation of tubular sodium reabsorption.

The regulation of renal sodium reabsorption in response to volume contraction is accompanied by a number of compensatory responses that modulate renal sodium reabsorption (Figure 2.5). A fall in peritubular capillary and an increase in peritubular capillary protein concentration oncotic pressure increase proximal tubular sodium absorption. Increased renal nerve activity also augments sodium reabsorption in the proximal tubule, thick ascending limb of Henle's loop, and in the distal tubule. Circulating angiotensin II levels increase and stimulate both proximal tubule sodium transport and the release of aldosterone, which increases the sodium reabsorption in the collecting duct. The release of ADH also increases sodium reabsorption within the thick ascending limb of the loop of Henle and the cortical collecting duct.

As would be expected, extracellular volume expansion is accompanied by alterations in peritubular physical factors that decrease proximal tubule sodium reabsorption (Figure 2.6). These changes include a fall in peritubular protein concentration and a rise in peritubular hydrostatic pressure. Renal sympathetic nerve activity diminishes, which also depresses tubular sodium reabsorption. The fall in renal nerve activity also depresses transport in the thick ascending limb of Henle's loop and distal tubule. Lower circulating angiotensin II levels decrease both proximal transport and the release of aldosterone. A fall in aldosterone also decreases sodium reabsorption in the collecting duct.

Dehydration

The diagnosis and management of perturbations in the extracellular fluid volume constitute an important aspect of medical care of children. Dehydration, often resulting from gastroenteritis is by far the most common disturbance of fluid volume encountered in children.

Diagnostic evaluation

Pertinent history and physical findings of dehydration are outlined in Table 2.3. Whenever possible, assessment of volume status should include an evaluation of any recent changes in body weight. With mild volume depletion (3–5%), patients are thirsty, have dry mucous membranes, and have a decreased urine output. Moderate degrees of volume depletion (6–10%) are associated with poor skin turgor and poor perfusion, sunken eyes or fontanelle, tachycardia, orthostatic changes in blood pressure, and irritability or listlessness. In addition to these

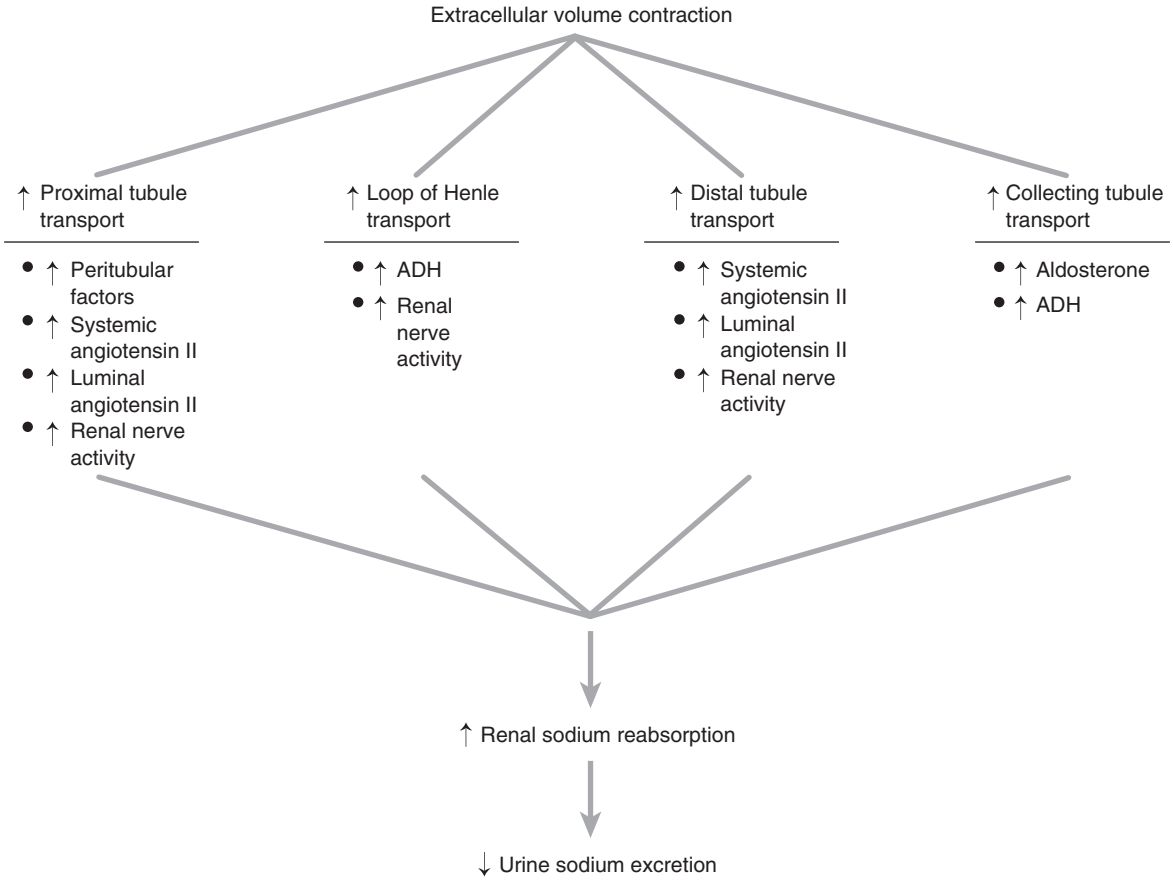

Figure 2.5 Renal responses to extracellular fluid volume depletion. ADH, antidiuretic hormone.

findings, severe volume depletion (>10%) is associated with hypotension, lethargy, or coma.

Management of volume depletion

The goal in the treatment of perturbations of the extracellular volume is to restore normal extracellular volume so as to maintain adequate cardiovascular function. During extracellular volume depletion, cardiovascular and hemodynamic stability must first be restored. In most clinical scenarios of acute volume depletion – i.e. diarrhea, vomiting, or an acute febrile illness – the fluid loss occurs primarily from the extracellular fluid compartment. Correction of this volume loss, therefore, consists of volume replacement with a replacement fluid that has a composition similar to the extracellular fluid. In the initial resuscitation phase of correction of dehydration, a bolus of isotonic fluid (normal saline or Ringer's lactate) should be administered to restore hemodynamic stability. Alternatively, a colloid solution, such as 5% albumin may be considered in moderate to severe volume depletion. These fluid boluses serve to restore tissue perfusion and cardiovascular function.

The second phase of fluid resuscitation focuses upon replacement of the rest of the fluid deficit, and providing maintenance fluids. Maintenance fluid requirements provide fluid, sodium, and potassium to replace daily normal ongoing losses, including insensible water loss through skin and respiratory tract and normal urinary water, sodium, and potassium losses. The sodium content required for maintenance fluid is 2–3 mEq/100 ml of maintenance fluid and the amount of potassium required is 2 mEq/100 ml of maintenance of fluid. Potassium should never be given until urine output has been established and the serum creatinine evaluated. Maintenance fluid requirements for children with normal renal function are outlined in Table 2.4. During the second phase of fluid resuscitation (approximately 8 hours), fluid provided consists of replacement of one-half of the deficit along with maintenance fluids. In the third and final phase of fluid resuscitation, the remaining one-half of the deficit is given along with the maintenance fluids over a 16-hour period. During fluid resuscitation, the patient should be monitored frequently. In addition, urine output should be carefully followed and electrolytes need to be periodically evaluated.

Clinical case

A 3-year-old boy presented with a 2-day history of diarrhea and decreased oral intake. According to his mother, he was urinating less frequently, but had urinated just prior to coming to the clinic. His 6-year-old sister had diarrhea 5 days ago that had now resolved. The boy's weight in the clinic 2 weeks

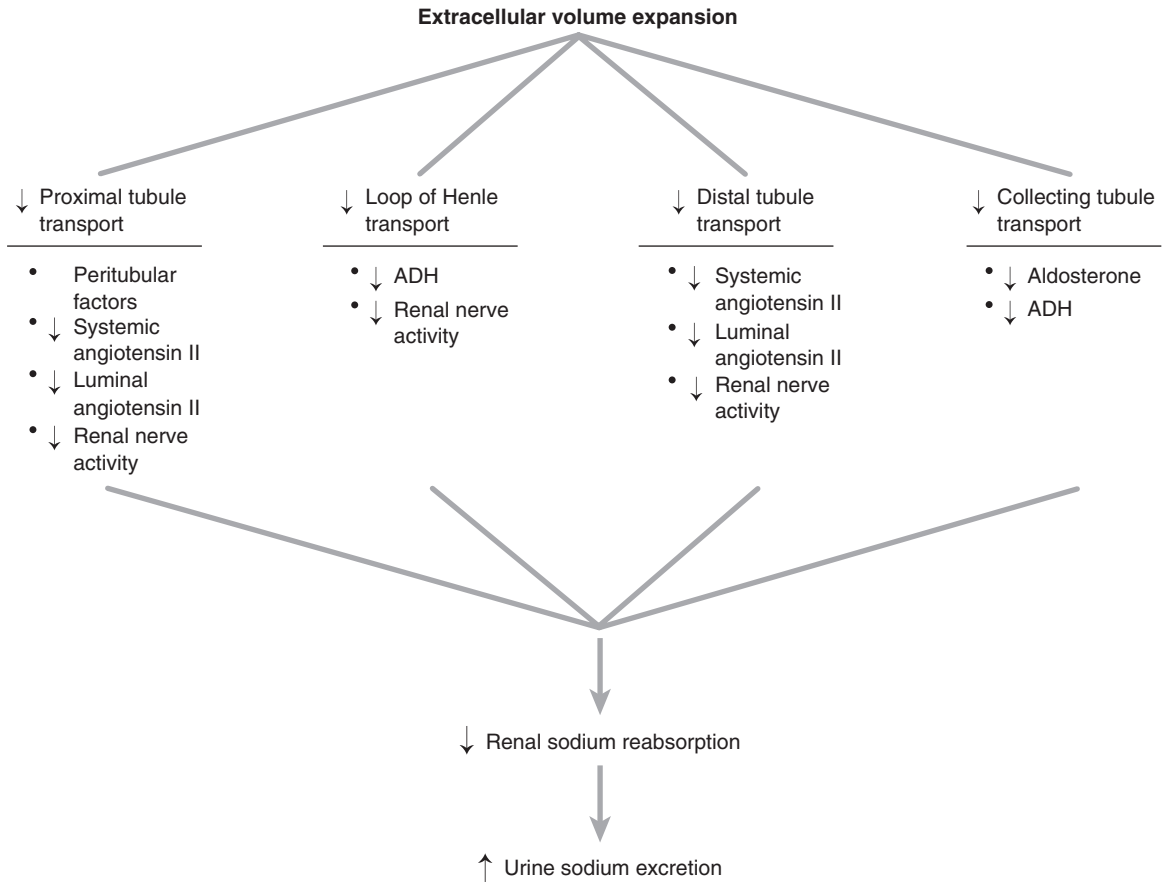

Figure 2.6 Renal responses to extracellular fluid volume expansion. ADH, antidiuretic hormone.

Table 2.3 Extracellular volume depletion

Condition	History	Physical findings
Mild (3–5%)	Thirst Decreased urine output	Dry mucous membranes
Moderate (6–10%)	Thirst Decreased urine output Change in mental status	Dry mucous membranes Sunken eyes Sunken fontanelle Postural hypotension Tachycardia
Severe (>10%)	Decreased urine output Lethargy Coma	Dry mucous membranes Sunken eyes Sunken fontanelle Poor perfusion – cool extremities Hypotension Tachycardia

ago was 15 kg, but today was at 14.25 kg. His vital signs were: heart rate, 120 beats/min; respiratory rate, 29 breaths/min; temperature, 36.9°C; and blood pressure, 90/40 mmHg. On physical examination, he was irritable, but consolable by his mother, and his mouth and tongue were dry. He had only scant tears when crying. The remainder of the examination was unremarkable. On laboratory evaluation, his electrolytes were: Na, 140 mmol/L; K, 3.4 mmol/L; Cl, 105 mmol/L; CO_2,

Table 2.4 Daily maintenance fluid and solute requirement

Body weight	Fluid	Sodium	Potassium
1–10 kg	100 ml/kg	2–3 mEq Na/100 ml	2 mEq K/100 ml
11–20 kg	1000 ml + 50 ml/kg for each kg >10 kg	2–3 mEq Na/100 ml	2 mEq K/100 ml
> 20 kg	1500 ml + 20 ml/kg for each kg >20 kg	2–3 mEq Na/100 ml	2 mEq K/100 ml

22 mmol/L; and his BUN and creatinine levels were 20 mg/dl and 0.6 mg/dl, respectively.

Comment
This child had acute extracellular volume depletion due to diarrhea and decreased oral intake. The degree of volume depletion can be approximately calculated from his weight loss (15 kg – 14.25 kg) and is 750 ml (0.75 kg) or 5% volume depletion. His physical examination was consistent with 5% volume depletion. To formulate a plan for fluid resuscitation, it is best to consider his fluid and sodium requirements for both deficit replacement and maintenance:

- His volume deficit was 750 ml of isotonic volume, which would contain 140 mmol NaCl/L or a total of 105 mmol Na (0.75 L × 140 mmol Na/L).
- His maintenance fluids were 1250 ml/day or 52 ml/h [(100 ml/kg × 10 kg) + (50 ml/kg × 5 kg)]. His daily Na requirement is ~40 mmol Na/day (3 mmol Na/100 ml × 1250 ml). His daily K requirement is ~25 mmol K/day (2 mmol K/100 ml × 1250 ml).
- His total fluid requirement to replace deficit and maintenance fluids is 2000 ml (750 ml + 1250 ml). The Na requirement for maintenance and deficit is 145 mmol (105 mmol + 40 mmol) Na. This yields 145 mEq Na in 2000 ml of fluid or approximately 1/2 NS as replacement fluid. Replacement of half of his fluid deficit over the first 8 hours requires a fluid rate of ~50 ml/h [(750 ml × ½)/8 h]. Maintenance fluids are run at ~50 ml/h, as mentioned above. This gives him a combined fluid rate of 100 ml/h (50 ml/h + 50 ml/h) for the first 8 hours. The second 16-hour period would consist of maintenance at 50 ml/h + (750ml × ½/16h = 25ml/h for the remaning deficit repletion) to equal a total of 75ml/h. During fluid resuscitation, he should be closely monitored for hemodynamic stability. Electrolytes should be periodically checked. K can be added at 20 mEq KCl/L once it is sure that he has good renal function and is not hyperkalemic.

Edema

Definition

Edema refers to the excessive accumulation of extracellular fluid in the interstitial space. Symptoms of puffiness of the eyelids, swelling of feet, and abdominal distention are common manifestations of edema. Although swollen eyelids are generally more prominent in the morning, pedal swelling is worse after a period of ambulation, usually at the end of the school- or workday. Ascites can be particularly severe in patients with liver disease.

Pathophysiology of edema formation

The physiology of edema formation involves the forces governing plasma–interstitial fluid exchanges (Starling forces), as seen in Figure 2.7. The components include the hydraulic and oncotic pressures originating from within the capillary lumen and the opposing hydraulic and oncotic pressures originating from the interstitium surrounding the capillary. The capillary hydraulic pressure (P_c), derived from the arteriolar pressure, is higher than the interstitial hydraulic pressure (P_i) and favors movement of fluid from the capillary into the interstitial space. Capillary oncotic pressure (π_c), derived from serum albumin, is higher than interstitial oncotic pressure (π_i) and retards the movement of fluid out of the capillary into the interstitium. Under normal conditions, the summation of the hydraulic and oncotic forces favors a small movement of fluid (and sodium) out of the capillary into the interstitium. This ultrafiltered interstitial fluid is returned into the general circulation via the lymphatic channels. The formation of edema occurs when there is a perturbation in one or more of the Starling forces, resulting in excessive accumulation of interstitial fluid. Clinically, edema occurs in three pathophysiologic states: congestive heart failure, hepatic cirrhosis, and nephrotic syndrome.

Congestive heart failure

Heart failure results in a decrease in cardiac output and the effective circulating volume. In turn, these result in an increase in renal nerve activity, activation of the renin– angiotensin axis, and increase in aldosterone levels. The end result of these pathophysiologic alterations is increased renal sodium and water reabsorption, resulting in edema formation. In addition, higher cardiac filling pressures are transmitted to the capillary bed, raising the capillary hydrostatic pressure (P_c), which alters the capillary Starling forces, favoring an increase in net fluid movement out of the capillary into the interstitium as edema.

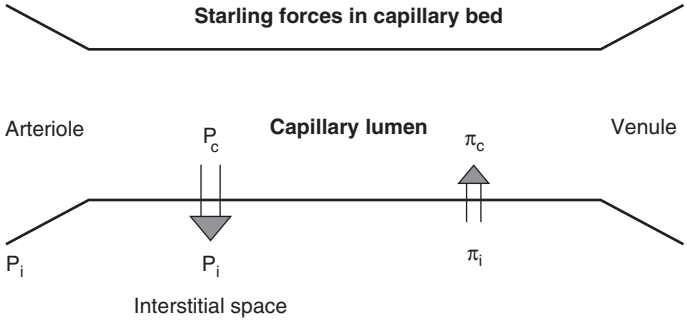

Figure 2.7 Starling forces in capillary bed: the capillary hydraulic pressure (P_c), derived from the arteriolar pressure, is higher than the interstitial hydraulic pressure (P_i) and favors movement of fluid from the capillary into the interstitial space. Capillary oncotic pressure (π_c), derived from serum albumin, is higher than interstitial oncotic pressure (π_i) and retards the movement of fluid out of the capillary into the interstitium. Under normal conditions, the sum of the hydraulic and oncotic forces favors a small movement of fluid (and sodium) out of the capillary into the interstitium. This ultrafiltered interstitial fluid is returned into the general circulation via the lymphatic channels.

Treatment includes removal of the excessive fluid by use of diuretics and increasing cardiac output.

Cirrhosis

Several factors contribute to the accumulation of edema with cirrhosis. First, cirrhosis and portal fibrosis impair hepatosplanchnic circulation, leading to increased capillary hydraulic pressure, and ultimately resulting in formation of ascites. Secondly, liver injury reduces serum albumin production, with resultant decrease in the capillary oncotic pressure, favoring the transudation of fluid into the interstitial space and edema formation. In addition, the formation of systemic arteriovenous malformations in the microcirculation further reduces the effective circulating volume, which results in augmented renal sodium reabsorption. The cumulative effect of these three factors results in a prominent development of ascites and peripheral edema.

Nephrotic syndrome

Hypoalbuminemia in nephrotic syndrome leads to a loss of capillary oncotic pressure and altered Starling forces, which favors accumulation of interstitial edema. As a result of a fall in effective circulating volume, renal sodium reabsorption secondarily rises and further exacerbates the formation of edema. Edema generally becomes more marked as the serum albumin falls below 2 g/dl.

Nephrotic syndrome in adults and older children may be due to lesions other than minimal-change nephrotic syndrome. The intravascular volume in these patients may be actually increased. Edema formation in such patients is primarily due to renal sodium absorption and results from poorly understood factors.

Potassium balance

Potassium is the most abundant intracellular cation. Maintenance of the steep potassium concentration gradient between the intra- and extracellular fluid is accomplished by the ubiquitous Na^+/K^+-ATPase. The potassium concentration in the extracellular fluid is tightly regulated by mechanisms that govern the distribution of the ion between the intracellular and extracellular compartments, as well as the external balance between intake and output.

Potassium homeostasis

The homeostatic goal of the adult is to remain in a net zero potassium balance. Thus, ~90–95% of the daily intake of this cation is ultimately eliminated from the body in the urine. The remaining 5–10% of the daily potassium load is removed through the stool. Normally, the amount of potassium lost through the sweat is negligible. After ingestion of a potossium containing meal the renal excretion of potassium is sluggishing, requiring several hours to be accomplished. However, life-threatening hyperkalemia is prevented during this period due to the rapid translocation of extracellular potassium into the cells, particularly muscle and liver, by various hormones. Among the hormones that stimulate the cellular uptake of potassium are insulin, β_2-adrenergic agonists and aldosterone.

Potassium is freely filtered at the glomerulus. Approximately 65% of this filtered load of potassium is passively reabsorbed along the proximal tubule, closely following water reabsorption. An additional 20–30% of the filtered load of potassium is reabsorbed along the thick ascending limb of the loop of Henle by the $Na^+/K^+/2Cl^-$ cotransporter described above. Potassium reabsorption in the proximal tubule and ascending limb is ultimately driven by the Na^+/K^+-ATPase present at the basolateral membrane. By the time the tubular fluid reaches the distal convoluted tubule, as little as 10% of the filtered potassium remains in the luminal fluid.

Under physiologic conditions, potassium secretion by the distal nephron, including the connecting tubule and collecting duct, contributes prominently to urinary potassium excretion. Potassium secretion requires that this ion be actively transported into principal cells in exchange for sodium by the basolateral Na^+/K^+ pump (see Figure 2.1). Potassium accumulates within the cell and then passively diffuses across the apical membrane through secretory potassium channels, including ROMK in the thick ascending limb of the loop of Henle, and, under conditions of high urinary flow rate, a calcium- and stretch-activated maxi-K channel.

The magnitude of potassium secretion in the distal nephron is determined by the electrochemical gradient that is generated by the potassium concentration gradient between the cell and urinary space and the lumen negative voltage that is established by the electrogenic absorption of urinary sodium through ENaC, unaccompanied by a negatively charged anion. Factors that enhance the electrochemical driving force, such as an

increase in tubular flow rate following diuretic administration or high circulating levels of mineralocorticoids (which increase the apical membrane permeability to sodium and potassium), will promote potassium secretion.

The direction of net potassium transport in the distal nephron varies according to physiologic needs. In response to potassium depletion, as may result from dietary potassium restriction, the distal nephron may reabsorb potassium. Potassium reabsorption under these circumstances is mediated by an H/K-ATPase, an enzyme that exchanges a single potassium ion for a proton, residing on the urinary surface of intercalated cells.

Postnatal growth is associated with an increase in total body potassium from ~8 mEq/cm body height at birth to >14 mEq/cm body height by 18 years of age.[46] Therefore, in order to support growth, newborns must conserve potassium. The neonatal kidney, and specifically the distal nephron, is uniquely positioned to retain urinary potassium, as it has few potassium secretory channels and a relative surfeit of H/K-ATPase activity.

Hypokalemia

Hypokalemia, defined as a serum potassium concentration of less than 3.5 mEq/L, generally indicates a deficit in total body potassium, but may simply reflect a transcellular shift of the cation from the extra- to the intracellular space in the presence of normal body potassium stores. Clinical disorders associated with potassium redistribution and depletion are listed in Table 2.5.

Table 2.5 Clinical disorders associated with hypokalemia

- Pseudohypokalemia
- Transcellular shift of potassium into cells:
  - Acute alkalosis (metabolic, respiratory)
  - Insulin administration
  - β-adrenergic agonists (epinephrine, albuterol, terbutaline), dopamine, theophylline
  - Hypokalemic periodic paralysis
  - Barium poisoning
- Inadequate intake
- Renal loss:
  - Diuretics:
    - Thiazides and loop diuretics
    - Osmotic diuretics (mannitol, glucose)
    - Carbonic anhydrase inhibitors
  - Diabetic ketoacidosis
  - Excess mineralocorticoid activity
    - Primary hyperaldosteronism:
      - Aldosterone-producing adenomas
      - Bilateral adrenal hyperplasia
      - Glucocorticoid-remediable aldosteronism
    - Cushing's syndrome:
      - Primary adrenal
      - Secondary to non-endocrine tumor
    - Pharmacological doses of corticosteroids
    - Excessive licorice ingestion
  - Excessive renin production
  - Renal tubular transport defects:
    - Bartter syndrome
    - Liddle syndrome
    - Gitelman syndrome
  - Miscellaneous:
    - Magnesium deficiency
    - Antibiotics: -cillin antibiotics, gentamicin, polymyxin B, amphotericin
    - Leukemia
- Gastrointestinal loss:
  - Vomiting
  - Diarrhea
  - Biliary drainage
  - Villous adenoma
  - Ureterosigmoidostomy
  - Laxative or enema abuse
- Integumental loss:
  - Excessive sweating
  - Full-thickness burns

Clinical manifestations

The consequences of potassium depletion affect many organ systems and depend, in part, on the magnitude and duration of the deficit. The most prominently affected organs are the neuromuscular system, the cardiovascular system, and the kidneys.

The ratio of potassium concentration in cells to that in the extracellular fluid is the major determinant of the resting membrane potential (E_m) across the cell membrane. Given that E_m in large part determines neuromuscular excitability, alterations in the distribution of potassium across the cell membrane can have dramatic consequences for excitable cells. A rapid reduction in the extracellular potassium concentration (leading to a high ratio of intra- to extracellular potassium) increases or hyperpolarizes E_m, thereby making the cell less excitable. This neuromuscular dysfunction manifests as skeletal muscle weakness and, in severe cases, is associated with frank paralysis. Death may follow due to respiratory muscle failure. Hypokalemia-induced smooth muscle dysfunction is usually manifest as paralytic ileus and diminished ureteral peristalsis.

Hypokalemia contributes to cardiovascular morbidity and mortality due to its impact on cardiac conduction and arterial blood pressure. The electrical disturbances of conduction and rhythm, manifest on the electrocardiogram as depression of the S-T segment, diminished T wave voltage and appearance of the U wave, generally appear at plasma potassium levels of less than 3 mEq/L. In patients with heart failure, cardiac ischemia, left ventricular hypertrophy, or on digoxin therapy, hypokalemia significantly increases the risk of cardiac arrhythmias.

The most common abnormality of renal function associated with potassium depletion is the inability to maximally concentrate the urine, a deficit arising from a reduced osmolar

gradient in the medullary interstitium. This concentrating deficit is resistant to the administration of exogenous vasopressin, as well as prolonged water deprivation. Hypokalemia impairs activation of renal adenylate cyclase, preventing vasopressin-stimulated urinary concentration. In addition to this direct renal effect, potassium depletion stimulates the central thirst center via increased production of angiotensin II. The resultant polydipsia of severely hypokalemic subjects further increases urinary output and exacerbates the concentrating defect.

Diagnostic evaluation

The evaluation of a child with hypokalemia should begin with a detailed history that includes the pattern of growth, occurrence of chronic illness, family history of similar disease, use of drugs, and symptoms associated with the present electrolyte disturbance. Physical examination must include measurement of growth indices and blood pressure and assessment of any evidence of edema and altered neuromuscular function.

The initial laboratory evaluation should include measurement of serum electrolytes and acid–base status. Recent use of insulin (evidenced by hypoglycemia) and metabolic alkalosis can cause intracellular shift of potassium and pseudohypokalemia. If the serum is not promptly separated from the blood in patients with severely elevated leukocyte count (myeloid leukemia), the abnormal leukocytes take up potassium, leading to pseudohypokalemia. A complete blood count will help differentiate this diagnosis. If pseudohypokalemia is ruled out by the above laboratory studies, then hypokalemia is likely to reflect total body potassium depletion due to losses from the gastrointestinal tract, the kidneys, or skin.

A low urinary potassium concentration (<15 mmol/L) in the absence of recent diuretic use implies near-maximal urinary potassium conservation, suggesting extrarenal losses of potassium or inadequate intake. Gastrointestinal potassium loss can result from vomiting, diarrhea, internal fistulas, nasogastric suction, or a villous adenoma. Laxative abuse should be considered in patients overly concerned with their body image.

A child with a high urinary potassium excretion (>15 mmol/L, or a urinary sodium-to-potassium ratio consistently less than 1 in the absence of renal failure) is likely to have renal potassium wasting. Hypokalemia associated with hypertension and metabolic alkalosis is classically found in hyperreninemic states, such as renal vascular stenosis, and primary hyperaldosteronism. The finding of hypokalemia and metabolic acidosis in a normotensive patient should suggest renal tubular acidosis (RTA) or diabetic ketacidosis. Bartter syndrome and Gitelman syndrome should be considered in patients with hypokalemic metabolic alkalosis, chronic urinary sodium and chloride wasting, volume depletion, hyperreninemia, and hyperaldosteronism.

Management of hypokalemia

The choice of potassium replacement therapy depends on the magnitude of the potassium deficit.[47] Estimates of the degree of total body potassium depletion can only be made from plasma or serum values. It is important to note that serum potassium concentration, at best, represents an approximation of the total body stores. Therefore, treatment of the deficit, particularly in the presence of complicating factors that affect the transcellular distribution of potassium (e.g. acid–base status), must be performed cautiously, especially in patients with renal or cardiac disease.

Mild hypokalemia will often respond simply to dietary supplementation with foods containing high potassium content. Oral potassium supplements are necessary for moderate potassium depletion. Among the oral preparations available in liquid, powder, and slow-release preparations are potassium chloride, potassium citrate, and potassium gluconate. The latter two formulations are ideal for patients with a concomitant acidosis in whom the organic anion provides potential alkali. The adverse effects associated with oral therapy, especially following administration of potassium chloride, include gastrointestinal irritation, which can cause vomiting or even gastric ulceration.

Intravenous potassium supplementation therapy should be reserved for patients with severe hypokalemia, including those patients demonstrating neuromuscular or cardiac disturbances, and diabetics in ketoacidosis. Administration of potassium in dextrose-containing solutions may worsen the hypokalemia, by stimulating insulin secretion and intracellular shift of potassium. Parenteral potassium should be infused in a solution containing no more than 40 mEq/L and infused at a rate not to exceed 0.75 mmol/kg body weight in the first hour of therapy in children, or 10 mmol/h in adults. When life-threatening paralysis or ventricular arrhythmias are present, more aggressive potassium replacement may be appropriate.

In patients with diuretic-induced hypokalemia who require continued use of their diuretic, addition of a potassium-sparing diuretic such as amiloride, triamterene, or spironolactone should be considered. Hypomagnesemia can lead to renal potassium wasting and refractoriness to potassium replacement. Magnesium repletion facilitates correction of the coexisting potassium deficit.

Clinical case

An 18-year-old woman with a long-standing history of distal RTA and nephrocalcinosis developed gastroenteritis associated with vomiting and inability to tolerate oral fluids or medication (PolyCitra). One week into the illness, the patient collapsed at home, complaining of weakness. She was brought to the emergency room, where her initial evaluation revealed a heart rate of 60 beats/min, respiratory rate of 12 breaths/min, temperature of 37°C, and blood pressure of 70/30 mmHg. She had dry mucous membranes, cool extremities, and profound diffuse muscle weakness. An electrocardiogram (ECG) confirmed bradycardia and showed U waves. Laboratory evaluation revealed levels of serum bicarbonate of 11 mmol/L, potassium of

1.8 mmol/L, and creatinine of 1.5 mg/dl. Urinalysis revealed a specific gravity of 1.010 and pH 6.5.

Comment

This patient had intravascular volume depletion, not only as a result of the gastroenteritis but also because of her urinary concentrating defect that resulted from RTA-associated nephrocalcinosis and profound hypokalemia. The total body potassium depletion is manifest by the global neuromuscular dysfunction, affecting this patient's cardiovascular system as well as respiratory muscles. The therapy in the emergency room should consist of providing parenteral potassium and eventually replenishing the total body stores. Administration of bicarbonate at the onset can lead to a potentially life-threatening further decline in serum potassium concentration, and should be avoided until adequate potassium replacement has been achieved. Intravascular volume correction should also be addressed as a part of the treatment in the emergency room.

Hyperkalemia

Hyperkalemia is defined as a serum potassium concentration greater than 6.0 mEq/L in the newborn and 5.5 mEq/L in the older child and adult. However, the relationship between serum value and total body burden of potassium may not be obvious because the extracellular compartment contains so little of the total body potassium stores. For example, any abnormal transcellular shift of potassium to the extracellular fluid can result in hyperkalemia, a situation not accompanied by an increased total body content of potassium.

Etiology

Since the kidney provides the primary means of eliminating excess potassium, hyperkalemia is frequently observed with major disturbances of renal excretory function. A classification of disorders associated with hyperkalemia is presented in Table 2.6.

Table 2.6 Clinical disorders associated with hyperkalemia

- Pseudohyperkalemia
- Hematologic disorders: leukocytosis, thrombocytosis, test tube hemolysis
- Improper collection of blood
- Transcellular shift of potassium out of cells:
  - Metabolic acidosis
  - Insulin deficiency
  - Hyperosmolality
  - Succinylcholine
  - Digoxin overdose
  - Exercise with β-blockade
  - Arginine infusion
  - Familial hyperkalemic periodic paralysis
- Increased potassium load with compromised renal function
  - Exogenous:
    - Oral or parenteral potassium supplements
    - Salt substitutes
    - Potassium penicillin in high doses
    - Blood transfusion
  - Endogenous:
    - Intravascular hemolysis
    - Rhabdomyolysis
    - Exercise
    - Infection
    - Trauma
    - Burns
    - Tumor lysis
- Decreased renal excretory capacity:
  - Renal failure:
    - Acute
    - Chronic
  - Mineralocorticoid deficiency:
    - Addison disease
    - Hypoaldosteronism
      - Hyporeninemic
      - Specific enzymatic defects (21–hydroxylase, 18-hydroxydehydrogenase)
  - Impaired tubular secretion without abnormalities in mineralocorticoid production:
    - Sickle cell disease
    - Renal transplantation
    - Systemic lupus erythematosus
    - Lead nephropathy
    - Papillary necrosis
    - Obstructive and reflux uropathy
    - Pseudohypoaldosteronism
  - Drugs:
    - Potassium-sparing diuretics
    - Prostaglandin synthesis inhibitors
    - ACE inhibitors
    - Miscellaneous drugs

Clinical manifestations

The clinical consequences of hyperkalemia result from its adverse electrophysiologic effects on excitable tissues. Specifically, an increased extracellular potassium concentration brings the resting membrane potential closer to the action potential ('depolarizing block'). Thus, hyperkalemia may be manifest as skeletal muscle weakness, paresthesias, and ascending flaccid paralysis.

Although cardiac toxicity generally occurs when the serum potassium rises above 7 mmol/L, treatment should be initiated in any patient with suspected hyperkalemia if electrocardiographic abnormalities characteristic of hyperkalemia are noted. The first and most specific electrocardiographic abnormality seen with hyperkalemia is development of peaked T waves. The P-R interval lengthens and the QRS complex then widens. At potassium concentrations above 8 mmol/L, the P wave amplitude decreases, and may disappear with atrial standstill. As ventricular conduction time continues to lengthen, the QRS

complex merges with the peaked T wave, producing a 'sine wave' pattern. Finally, ventricular fibrillation or asystole may occur with potassium levels above 10 mmol/L.

Diagnostic evaluation

The work-up of a patient with hyperkalemia should include documentation of family history of hyperkalemia, the growth pattern, history of chronic illness, medication review, and daily intake. Since hyperkalemia is often asymptomatic, a history of neuromuscular dysfunction may not be elicited. Physical examination must include measurement of growth indices and blood pressure. Signs of chronic disease should be sought.

An ECG must be promptly obtained in any patient with hyperkalemia. Additional laboratory evaluation should include a repeat set of plasma (not serum) electrolytes with glucose, bicarbonate, and creatinine. Renal function can be further assessed with a urinalysis. An abnormal urinary specific gravity or pH may suggest a renal tubular defect, such as obstructive uropathy, whereas the presence of casts or large amounts of protein or red blood cells is consistent with glomerular disease. Information regarding renal potassium conservation can be obtained by measurement of urinary electrolytes. Patients with hypoaldosteronism or a tubular secretory defect will have a low fractional excretion of potassium despite progressive hyperkalemia. Finally, a complete blood count will reveal anemia, suggesting chronic renal failure, sickle cell disease, or leukemia.

Management of hyperkalemia

Treatment of hyperkalemia can be divided into three general categories:

- reversal of the membrane effects of hyperkalemia
- transfer of extracellular potassium into cells
- removal of potassium from the body.

Because the duration of action of each of these maneuvers differs, and because the first two measures are only temporizing, several treatment measures should be instituted simultaneously.

The effect of hyperkalemia on the cardiac cell membrane can be rapidly reversed with calcium. A rise in ionized calcium increases the threshold potential at which excitation occurs, thereby mitigating the depolarizing blockade resulting from hyperkalemia. Calcium gluconate (10%), the preparation most often employed, should be infused slowly intravenously with continuous electrocardiographic monitoring.

Somewhat more long-lasting effects (several hours) can be obtained by transferring extracellular potassium into cells, thereby re-establishing a more physiologic transmembrane potential gradient. This can be accomplished by inducing endogenous insulin release with a glucose infusion. Although insulin is generally also given, this may not be necessary in the absence of diabetes. The dose of glucose with or without insulin may be repeated as needed, monitoring for the complications of hyperglycemia (without insulin) or hypoglycemia (with insulin).

Administration of β_2-agonists (albuterol) via nebulizer, which promote potassium uptake by cells has been shown to be safe and efficacious. A single dose of nebulized albuterol can lower serum potassium by as much as 0.5 mmol/L. Transient side effects associated with this class of drugs include elevation of heart rate, tremor, and mild vasomotor flushing.

Although formerly recommended as a mainstay of therapy, alkalinization of the extracellular fluid with sodium bicarbonate to promote the rapid cellular uptake of potassium is no longer considered to be useful. However, this maneuver remains valuable if metabolic acidosis is present. Bicarbonate solutions should not be mixed with those containing calcium, due to the possibility of precipitating calcium carbonate. The major toxicities of bicarbonate therapy include sodium overload and precipitation of tetany in the face of pre-existing hypocalcemia.

Net potassium removal from the body in individuals with good renal function can be accomplished by stimulating flow-dependent potassium secretion in the distal nephron by administration of loop diuretics. In patients with renal insufficiency, a cation exchange resin may be administered to promote gastrointestinal elimination. Sodium polystyrene sulfonate (Kayexalate) is the resin used most commonly, given either orally or as a retention enema. Within the intestinal lumen, the resin binds 1 mmol of potassium in exchange for 1 mmol of sodium: 1 g/kg resin is expected to reduce the serum potassium by 1 mmol/L.

If the amount of potassium to be removed is of such magnitude that the administration of cation exchange resins does not suffice, dialysis may be necessary. Hemodialysis is the most efficient means of removing potassium in hyperkalemic patients. However, peritoneal dialysis is more widely available and more easily applied to pediatric patients than is hemodialysis. Continuous venovenous hemofiltration provides another means of removing total body potassium from hemodynamically compromised patients.

Conclusion

The kidneys play a key role in the regulation of the electrolyte, water, and acid–base homeostasis. The precise regulation of the internal milieu of the body involves interaction of the thirst mechanism, volume receptors, and numerous hormones, in addition to the complex coordination of the interdependent renal functions. Malfunction of any of these components can result in serious abnormalities of the fluid and electrolyte balance. An understanding of the physiologic principles that govern these intricate processes is essential for diagnosis and treatment of the clinical disorders of electrolyte and water balance. This chapter has provided an integrated approach to the understanding of these disorders, which the reader should find practical and useful in clinical practice.

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3 Disorders of mineral metabolism

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Mineral metabolism involves a complex interplay of ion and hormone control by individual organs in support of an overall total body homeostasis. The kidney is a pivotal participant in the maintenance of this homeostasis. This chapter discusses an overview of the metabolism and control of calcium, magnesium, and phosphorus ion balance. Common clinical disorders of the homeostasis of these ions and their management are also discussed.

Calcium metabolism

Calcium is a vital ion for many essential cellular metabolic functions and skeletal development. The regulation of calcium balance is a complex, multicompartmental interplay between the gastrointestinal tract, kidneys, and the skeletal system, and involves numerous hormones. Dietary calcium is absorbed actively from the proximal gastrointestinal tract, primarily in the duodenum and jejunum. The bioactive form of vitamin D, $1,25(OH)_2$ D, formed in the kidneys, is the sole hormonal stimulus for intestinal calcium transport. Additionally, passive flux of calcium from intestinal lumen to blood may occur through the concurrent absorption of simple sugars, even in the absence of active vitamin D, although much less efficient and not well regulated. The skeletal system is the major site of calcium storage (99%); only 1% being in the intracellular and extracellular compartment (Figure 3.1).

Within the plasma, 40% of the calcium is bound to plasma proteins and is non-ultrafilterable across the glomeruli. About 50% of serum calcium is found in the ionized form. The remainder (10%) of the calcium is complexed with anions, such as phosphate or carbonate. Of the plasma protein-bound fraction of calcium, 90% is bound to albumin and the remainder to globulins. Each gram of albumin, at the physiologic pH (7.4), binds 0.8 mg/dl of calcium. In the setting of hypoalbuminemia, the measured serum total calcium value must be corrected to account for low plasma albumin concentration. Corrected total serum calcium can be calculated in hypoalbuminemic patients by the formula:

$$\text{Corrected calcium (mg/dl)} = [4 - \text{plasma albumin (g/dl)}] \times [0.8 + \text{serum calcium (mg/dl)}]$$

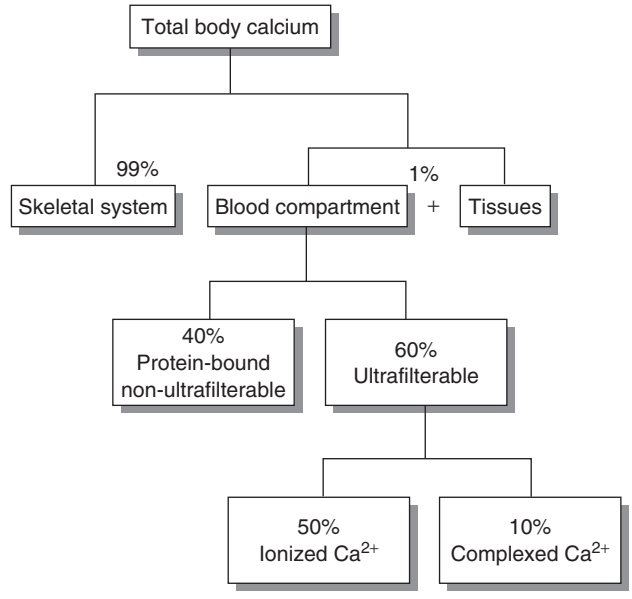

Figure 3.1 Distribution of calcium within various compartments in the body.

The ionized plasma calcium concentration is significantly affected by the acid–base status of the body. During acidemia (excess H^+) the negatively charged sites on the plasma proteins buffer the excess H^+, releasing calcium ions from these sites into the circulation, and raising the ionized calcium level. Alkalemia has the opposite effect of decreasing ionized calcium level.[1] The clinical implication of this phenomenon is that in a patient with metabolic acidosis and mild hypocalcemia, aggressive correction of metabolic acidosis can result in symptomatic hypocalcemia.

Renal handling of calcium

Both the ionized and the anion-complexed calcium are freely filtered across the glomerulus. In order to maintain a neutral calcium balance, the renal tubules must reabsorb most (98–99%) of the calcium from the glomerular ultrafiltrate. The proximal tubules reabsorb nearly 70% of the filtered calcium,

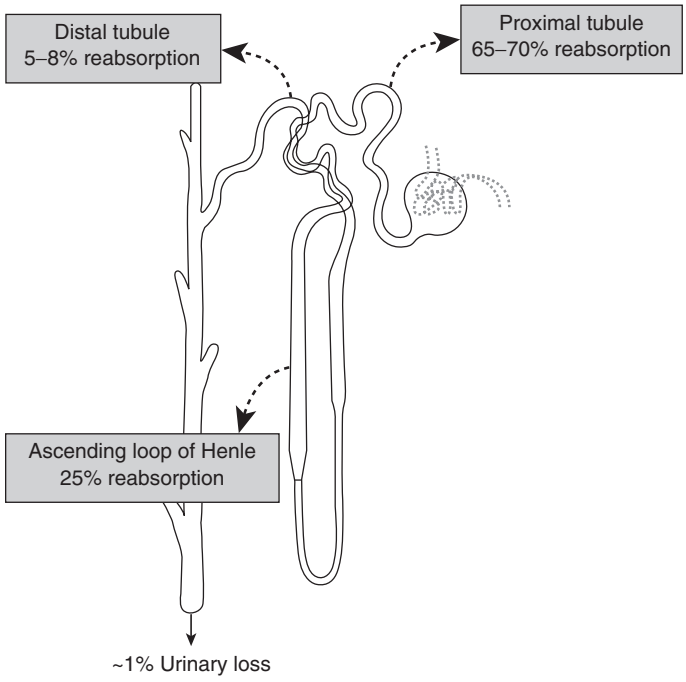

Figure 3.2 Sites of reabsorption of calcium in the nephron.

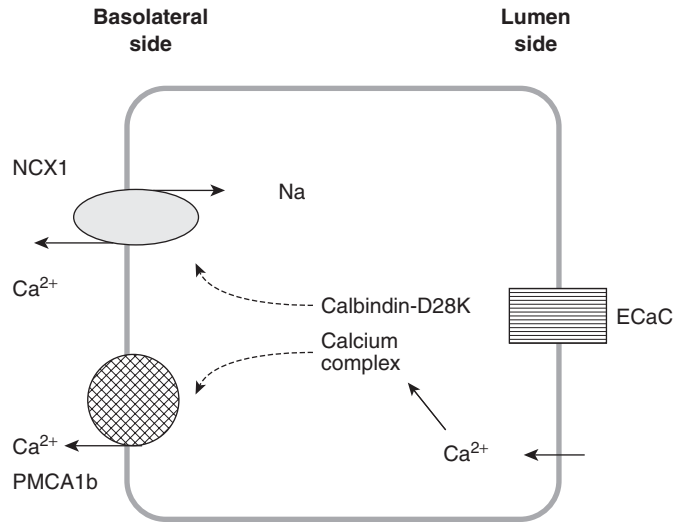

Figure 3.3 Diagrammatic representation of a distal tubular cell showing the mechanisms involved in the active tubular reabsorption of luminal calcium in this segment. The tubular cells in this nephron segment have calcium channels (ECaC) on the apical aspects, which facilitate transport of luminal calcium into the cell. Once within the cytosol, calcium combines with calcium-binding protein(s) calbindin-D28K that shuttles it to the basolateral aspect of the tubular cell. The sodium calcium exchanger 1 (NCX1) and the plasma membrane calcium ATPases (PMCA) pumps facilitate the transport of calcium out of the tubular cell at the basolateral surface.

largely by passive transport through paracellular solvent drag coupled to sodium and water (Figure 3.2).[2] The thick ascending limb of the loop of Henle reabsorbs about 25% of the filtered calcium load. The lumen in this portion of the nephron maintains a net positive charge due to the Na–K–2Cl transporter, which assists with reclaiming calcium through paracellular solvent drag. Remaining calcium in the ultrafiltrate is reabsorbed actively against an electrochemical gradient in the distal tubular segment made of distal convoluted tubule, collecting duct, and the cortical collecting tubule.[3] Fine-tuning of urinary calcium excretion is believed to occur by modulation of tubular calcium transport in this region. The tubular cells in the distal tubules have calcium channels (ECaC) on the apical aspects, which facilitate transport of luminal calcium into the cell (Figure 3.3). Once within the cytosol, calcium combines with a calcium-binding protein calbindin-D28K that shuttles it to the basolateral aspect of the tubular cell. Two active pumps – the sodium calcium exchanger 1 (NCX1) and the plasma membrane calcium ATPases (PMCA), subtypes 1 and 4[4] – help passage of calcium out of the cytosol at the basolateral aspect.

Calcium homeostasis

Calcium homeostasis is maintained by three key systemic hormones – the parathyroid hormone (PTH), calcitonin, and vitamin D – which act on the gastrointestinal tract, the kidneys, and the skeletal system (Table 3.1). To a large extent, the metabolic actions of these hormones are interrelated and interdependent.

Parathyroid hormone

PTH, an 84 amino acid-containing single-chain polypeptide, is produced by the chief cells of the parathyroid glands. The secretion of PTH from the parathyroid gland is regulated by the extracellular ionized calcium concentration. The cell membranes of the parathyroid gland chief cells have an extracellular calcium-sensing receptor (ECaR) that responds to plasma ionized calcium level.[5,6] A high plasma calcium level activates the ECaR and results in a decrease in PTH level, whereas a reduction in plasma calcium results in an inactivation of receptor function and increase in PTH secretion. A direct effect of plasma phosphorus on PTH synthesis and/or secretion remains controversial.

Acting on the skeleton, PTH stimulates the osteoclast-mediated release of calcium and phosphorus from the mineral matrix, in addition to providing a trophic action on bone mass accretion. In the kidney, PTH enhances calcium reabsorption in the distal tubular segment. It also inhibits the reabsorption of phosphate in the proximal convoluted tubule, resulting in phosphaturia. PTH increases the activity of the enzyme 25-hydroxyvitamin D 1α-hydroxylase in the proximal renal tubule and enhances the conversion of hydroxylated vitamin D 25~(OH)D to 1,25$(OH)_2$D in the kidney. This is the active form of the vitamin D endocrine system, and its biologic action leads to an increased intestinal calcium absorption. The impact of this metabolic process in raising plasma calcium concentration occurs over several days, in contrast to the impact of

Table 3.1 Hormonal mediators of calcium and phosphorus balance

Mediator	Stimulus for secretion	Renal response	Bone response	Gastrointestinal response	Net effect on serum calcium	Net effect on serum phosphorus
Parathyroid hormone (PTH)	Hypocalcemia	Decreased phosphorus reabsorption (phosphaturia) Increased calcium reabsorption Up-regulation of $1,25(OH)_2D$ production	Osteoclast activation and egress of calcium	Increased calcium absorption – through up-regulation of $1,25(OH)_2D$	An increase to normal values	A decrease from normal values
Calcitonin	Hypercalcemia	Increased calcium and phosphorus excretion	Inhibition of osteoclast activity	No effect	Decreased	Decreased
1,25-dihydroxy-vitamin D	Hypocalcemia, Elevated PTH Hypophosphatemia	Increased calcium and phosphorus reabsorption	Increased osteoclast activation	Increased calcium and phosphorus absorption	Increased	May increase to normal, stay normal, or decrease to values below normal
Phosphatonin(s) (FGF-23)	Excesses of dietary phosphorus intake	Decreased phosphate reabsorption (phosphaturia) Inhibition of 25-hydroxyvitamin D 1α-hydroxylase	Variable	Reduced calcium absorption due to effects on vitamin D	Unchanged	Normal or values below normal

PTH secretion, which materializes almost instantaneously (in minutes).

The overall impact of these PTH-dependent processes is to maintain the blood calcium and phosphorus in the normal range. Taking advantage of these discoveries in the control of calcium homeostasis, an allosteric ECaR agonist ('calcimimetic') agent, cinacalcet hydrochloride (Sensipar), has recently been introduced for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease.

Vitamin D

Vitamin D is either ingested in the diet or is produced from a common steroid precursor, 7-dehydrocholesterol, in the skin by the action of ultraviolet rays in the sunlight. Vitamin D ingested in the diet is absorbed in the proximal small intestine. For it to be biologically active, vitamin D undergoes hydroxylation in the liver at the carbon-25 position by the cytochrome CYP2R1 to form 25(OH)D (Figure 3.4). The transformed compound, 25(OH)D, undergoes further hydroxylation, at the carbon-1 position, in the kidney through the action of 25-hydroxyvitamin D 1α-hydroxylase, a specific mitochondrial P450 enzyme CYP27B1. Although earlier work had suggested that proximal renal tubule was the exclusive site of localization of the 1-α-hydroxylase activity,[7,8] recent observations using more sensitive probes suggest that the distal convoluted tubule, collecting duct, and papillary epithelia may also possess this enzyme activity.[9] 25(OH)D represents the largest circulating fraction of the vitamin D endocrine system, and serves as a measure of its nutritional status.

Following its synthesis in the kidney, $1,25(OH)_2D_3$ and other hydroxylated metabolites of vitamin D are transported in blood by the vitamin D-binding protein. The biologic actions of $1,25(OH)_2D_3$ are exerted after its binding to a specific paranuclear receptor in target cells known as the vitamin D receptor (VDR).[10] VDR has been found in virtually all cells, although its precise biologic functions in some of them are not fully understood.

Calcitonin

Calcitonin is a 32-amino acid-containing straight-chain peptide hormone produced by the parafollicular cells (also known as C cells) of the thyroid gland. Calcitonin demonstrates hormonal functions for modulating calcium and phosphorus

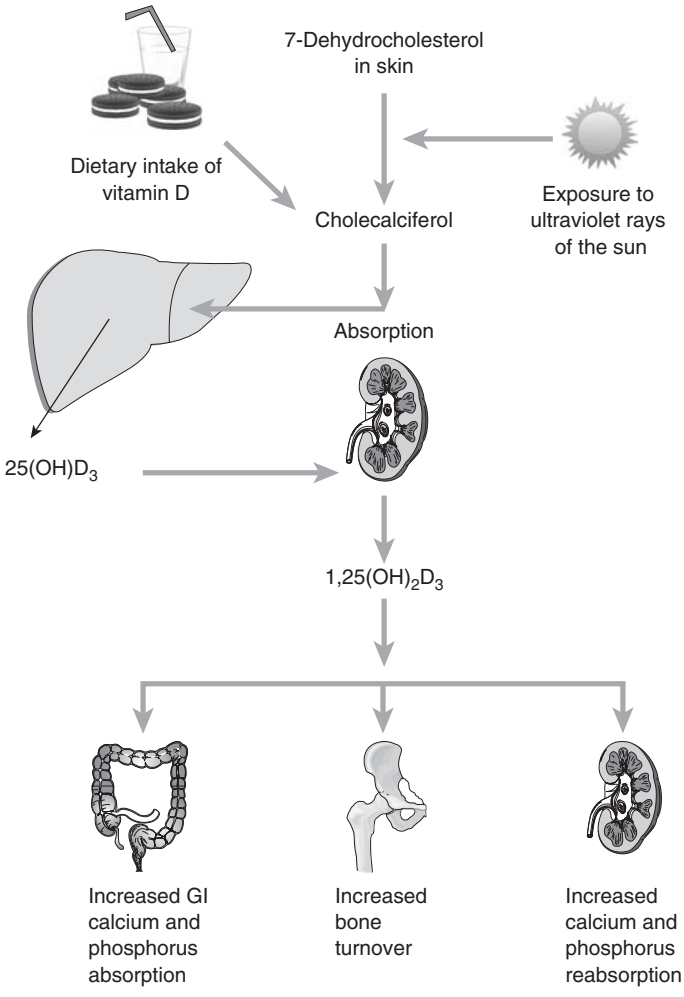

Figure 3.4 Schematic diagram showing bioconversion of vitamin D in the body and its primary biologic action in order to maintain calcium homeostasis.

metabolism, but its role as an important regulatory hormone in calcium metabolism is less than convincing. Like PTH, the primary target organs for the action of calcitonin are kidney and bone.[11] Calcitonin is secreted in response to increase in plasma calcium level. Its action on the bone is to inhibit bone resorption and consequently reduce serum calcium level. This physiologic action of calcitonin is sometimes used to treat hypercalcemia. In the kidneys, calcitonin action increases urinary calcium as well as phosphorus excretion, but the magnitude of its phosphaturic action is less than that seen with PTH.[12,13] Calcitonin also increases the renal production of $1,25(OH)_2D$.[14]

Hypocalcemia

Hypocalcemia is defined as a serum total calcium concentration of <8.8 mg/dl (2.2 mmol/L) in a patient whose serum albumin is normal, or when blood ionized calcium value is <4.2 mg/dl (1.05 mmol/L). Several formulas have been derived to 'normalize' the serum total calcium in hypoalbuminemic states, but none is superior to measurement of blood ionized calcium concentration. Broadly, hypocalcemia can be divided into disorders of parathyroid function, vitamin D metabolism, or of their receptors. Table 3.2 lists the common causes of hypocalcemia seen in infants and children.

Table 3.2 Causes of hypocalcemia

Artifactual
Low serum albumin
Use of gadolinium-based MRI contrast agent

Vitamin D-related
Lack of vitamin D:
- Nutritional
- Inadequate sunlight exposure
- Fat malabsorption

Defective vitamin D metabolism:
- Anticonvulsant therapy
- Renal disease
- Hepatic disease

Vitamin D-dependent rickets
- Type I, 25-hydroxyvitamin D 1α-hydroxylase deficiency
- Type II, inactiviating mutations of the vitamin D receptor (vitamin D resistance)

Parathyroid hormone-related
Lack of parathyroid hormone:
- Congenital hypoparathyroidism
- Post-parathyroidectomy
- Post-thyroidectomy
- Hypomagnesemia

Parathyroid hormone resistance:
- Pseudohypoparathyroidism

Clinical manifestations

The clinical manifestations of hypocalcemia are varied, and are determined by the severity and rapidity of its onset (Table 3.3). Whereas mild hypocalcemia may remain asymptomatic, progressive or rapid-onset hypocalcemia results in neuromuscular irritability and tetany. Alteration of consciousness and seizures may occur in severe cases.

Neuromuscular irritability due to hypocalcemia can be elicited by the Chvostek and Trousseau signs. The Chvostek sign is performed by tapping the jaw with a reflex hammer, or by a firm finger tap. A twitch elicited in response denotes a positive sign of neuromuscular irritability. It is important to note that the Chvostek sign is not specific for hypocalcemia. A Trousseau sign is elicited by applying a tourniquet or blood pressure cuff to the arm. A positive sign is indicated by carpal spasm following 3 minutes of inflation of the pressure cuff above the patient's systolic blood pressure. This sign is more specific for hypocalcemic tetany.

Table 3.3 Clinical manifestations of hypocalcemia

Neuromuscular irritability:
- Paresthesias
- Muscular weakness
- Carpopedal spasms
- Positive Chvostek and Trousseau signs
- Tetany
- Seizures

Cardiovascular dysfunction:
- Prolonged QT interval
- Arrhythmias
- Left ventricular dysfunction
- Hypotension
- Cardiomyopathy

Skeletal system:
- Poor bone mineralization
- Poor dentition

Miscellaneous:
- Neurosychiatric disturbances
- Papilledema

A prolonged QT interval is noted in most cases of mild to moderate hypocalcemia but other cardiac arrhythmias can be seen in severe cases of hypocalcemia.[15] Abnormalities of the electrocardiogram (ECG), mimicking myocardial infarction, have also been reported.[16] Long-standing hypocalcemia can result in digoxin-resistant left ventricular dysfunction and cardiomyopathy.[17,18] With long-standing hypocalcemia, abnormal dentition and cataracts may also be seen.

Clinical syndromes and conditions

Hypoparathyroidism

Hypoparathyroidism or a low circulating level of PTH results in hypocalcemia and hyperphosphatemia. A transient form of hypoparathyroidism may be seen in newborn infants through the second week of life. Risk factors for transient neonatal hypoparathyroidism include prematurity, low birth weight, infants of diabetic mothers, as well as babies born to mothers with hypercalcemia.[19]

Permanent forms of hypoparathyroidism occur in the velocardiofacial syndrome, which is a spectrum of disorders caused by gene deletions in chromosome 22q11.[20] These disorders include the DiGeorge anomaly, which is associated with cardiac and facial defects, in addition to thymic and parathyroid hypoplasia of varying degree. Familial hypoparathyroidism is a rare disorder that may be inherited as an isolated autosomal recessive, autosomal dominant, or X-linked recessive endocrinopathy.[21] Hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR) is a distinct disorder that is inherited as an autosomal dominant disease. It is associated with mutations in the dual zinc finger transcription factor, GATA3 (a transcription factor that specifically binds the DNA sequence A/T-GATA-A/G, hence the name GATA).[21,22] GATA3 is a transcription factor for vertebrate embryonic development. The molecular mechanism behind this defect causing HDR is still undetermined. Activating mutations in the calcium-sensing receptor gene have also been associated with hypoparathyroidism–hypocalcemia.[21,23]

Pseudohypoparathyroidism

After PTH attaches to its cellular receptors, it activates guanine nucleotide regulatory proteins (Gs), which in turn mediates activation of cyclic adenosine monophosphate (cAMP) for the cellular effects of PTH to be completed.[6] Pseudohypoparathyroidism is characterized by an end-organ resistance to PTH at the signal level. In a hypocalcemic patient findings of elevated circulating levels of PTH and hyperphosphatemia in the absence of renal dysfunction are characteristic findings of this disorder. Two types of pseudohypoparathyroidism have been described. Type I pseudohypoparathyroidism is characterized by an absence of normally function guanine nucleotide regulatory proteins (Gs). Type I pseudohypoparathyroidism includes McCune–Albright osteodystrophy, which is characterized by the clinical features of short stature, skeletal abnormalities, mental retardation, hypothyroidism, and hypogonadism, in addition to end-organ PTH resistance.[1,24] Type II pseudohypoparathyroidism is associated with a yet-unknown defect downstream from activation of cAMP.[25] No characteristic phenotype has been reported. The two types of pseudohypoparathyroidism are distinguished by urinary levels of cAMP in response to exogenous PTH infusion (Ellsworth– Howard test): in type I, urinary cAMP does not increase with stimulation; in type II, the urinary cAMP levels increase in response to PTH.

Hypomagnesemia

Magnesium is required for adequate release of preformed PTH from the parathyroid gland under conditions of hypocalcemia.[26] Moderate to severe hypomagnesemia may lead to low PTH levels. Peripheral resistance to the actions of PTH has also been considered a factor in the pathogenesis of hypocalcemia under these circumstances.[27] Correction of hypomagnesemia promptly results in correction of hypocalcemia and parathyroid resistance.

Vitamin D deficiency states

Vitamin D deficiency results in hypocalcemia, elevated PTH levels, hypophosphatemia, and hyperaminoaciduria. Nutritional vitamin D deficiency is common in the developing world. However, it is also being recognized increasingly in the Western world, especially in patients with malabsorption of vitamin D resulting from abnormalities of structure or function of the gastrointestinal tract.[28,29] Liver diseases with an inability to 25-hydroxylate the parent vitamin D may also lead to vitamin D deficiencies rickets and hypocalcemia. Apart from hypocalcemia and hypophosphatemia, diminished levels of 25-hydroxyvitamin D are the hallmarks of vitamin D deficiency rickets.

Radiographs of the skeleton demonstrate the characteristic findings of rickets. Treatment consists of providing vitamin D supplements, but those with liver disease may require therapy with $1,25(OH)_2D_3$ (calcitriol). Healing of radiographic skeletal abnormalities can be noted as early as 6–8 weeks, but may require 12–16 weeks.

Vitamin D-dependent rickets

Vitamin D-dependent rickets (VDDR) are rare metabolic disorders that are characterized by hypocalcemia and all of the clinical and biochemical features of rickets. Two types of VDDR have been described (Figure 3.5). VDDR type I, also known as pseudovitamin D deficiency rickets, is an autosomal recessive disease associated with markedly diminished or absent synthesis of $1,25(OH)_2D$ due to deficiency of the 25-hydroxyvitamin D_3 1α-hydroxylase enzyme in the kidney. Numerous mutations in the *CYP27A1* gene that encodes 25-hydroxyvitamin D_3 1α-hydroxylase in the kidney have been described in association with this disorder.[30] Patients with VDDR type I present in early infancy with muscle weakness, bony deformities (rickets), and hypocalcemic seizures.[31] The plasma level of $1,25(OH)_2D$ is low or absent, while the $25(OH)D_3$ level is elevated or normal. Exogenous administration of a physiologic dose of $1,25(OH)_2D_3$ (calcitriol) is able to correct the clinical, radiologic, and biochemical abnormalities associated with this disorder.

VDDR type II is characterized clinically by the presence of bony deformities characteristic of rickets, poor linear growth, early onset of alopecia, and loss of teeth.[32] Some patients may not, however, have alopecia.[33] Apart from hypocalcemia, patients have severe hyperparathyroidism and a high circulating level of $1,25(OH)_2D_3$. VDDR type II is caused by mutations in the vitamin D receptor gene.[34,35] Patients demonstrate end-organ resistance to vitamin D and are resistant to high-dose vitamin D therapy and supplementation with $1,25(OH)_2D_3$ (calcitriol). Long-term intravenous calcium supplementation has been shown to be effective in the treatment of VDDR type II.[36]

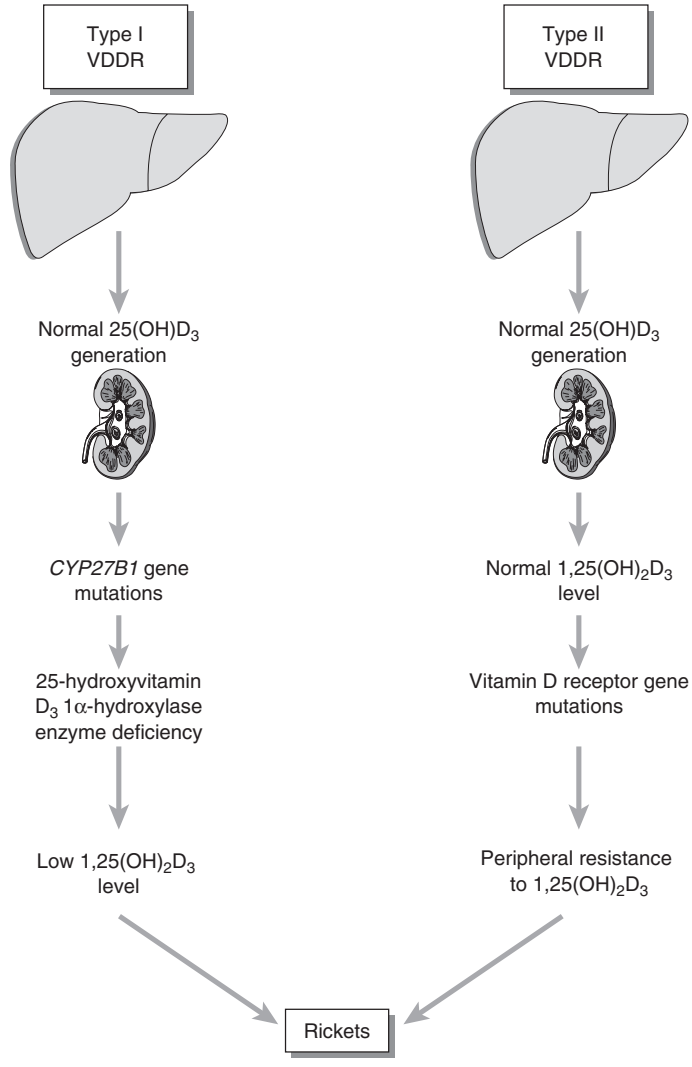

Figure 3.5 Schematic representation of the pathogenesis of type I and type II vitamin D-dependent rickets (VDDR).

Evaluation of hypocalcemia

An evaluation of hypocalcemia should include concurrent measurement of serum phosphorus, an evaluation of acid–base status (free-flowing venous blood is acceptable), serum intact or biointact PTH levels, levels of 25-(OH)D, $1,25(OH)_2D$ serum magnesium, and evaluation of renal function. Urinary excretions of minerals and electrolytes may be needed in some circumstances as well. Figure 3.6 provides an algorithm for evaluation of children with hypocalcemia.

Serum phosphorus

Determination of serum phosphorus concentration aids in distinguishing the etiology of low serum calcium levels beyond the neonatal age. In neonates, the serum phosphorus level is normally higher as a result of the limited ability of the neonatal kidney to excrete phosphorus in a fashion similar to that in older children. Hypocalcemia, coupled with hypophosphatemia, often points to an abnormality in vitamin D metabolism, whereas the presence of hyperphosphatemia points to a diagnosis of hypoparathyroidism, pseudohypoparathyroidism, or renal failure.

Serum magnesium

Magnesium is required for the secretion of PTH from the parathyroid gland and should be evaluated in patients presenting with previously undiagnosed hypocalcemia. Hypomagnesemia may be an important etiology of hypocalcemia, especially in neonates.

Parathyroid hormone

An elevated serum level of PTH may be seen in pseudohypoparathyroidism, chronic renal failure, vitamin D deficiency, or

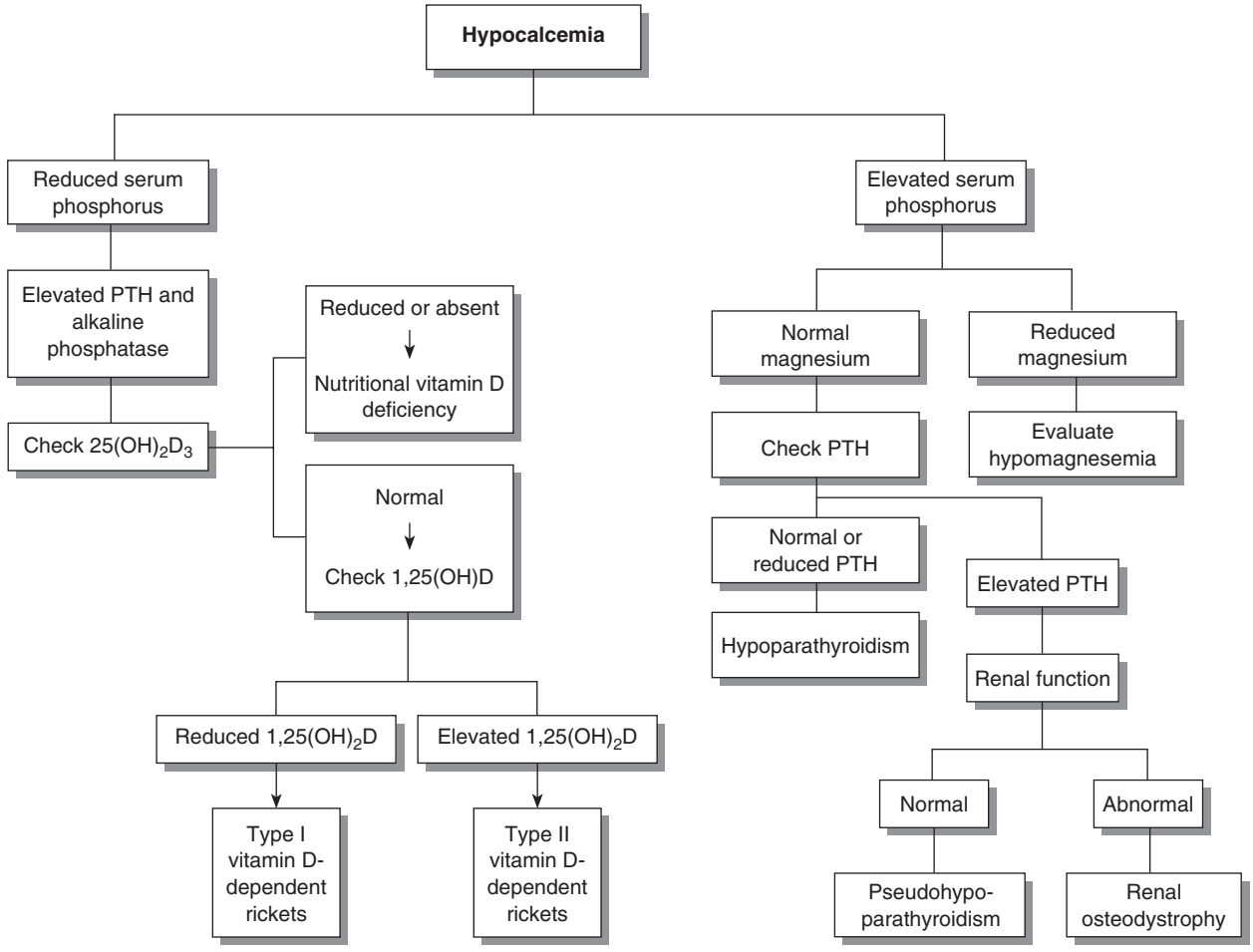

Figure 3.6 A suggested algorithm for evaluation of children with hypocalcemia.

in other abnormalities of vitamin D metabolism. Low levels point to hypoparathyroidism. If an elevated PTH level is found in the setting of hypocalcemia, then assessment of kidney function should be sought in the diagnostic evaluation.

Vitamin D level

Hypocalcemia in the setting of hypophosphatemia, coupled with elevations of serum PTH and alkaline phosphatase activity, suggests a disorder of vitamin D metabolism. Measurement of circulating levels of 25(OH)D and $1,25(OH)_2D$ should be performed in order to determine any defects in the metabolic pathways of vitamin D.

Treatment of hypocalcemia

Treatment of hypocalcemia is usually urgent, especially in sick patients with neuromuscular irritability or seizures. Intravenous calcium therapy is required in these patients, whereas milder hypocalcemia may be amenable to oral treatment. Therapy also needs to be tailored to the underlying etiology and pathogenesis of hypocalcemia.

Calcium supplements

Oral calcium supplements – phosphate, citrate, and acetate salts of calcium – are often used for long-term restoration and maintenance of blood calcium levels. The elemental calcium content of these salts is variable. In general, the gastrointestinal calcium absorption rate is highly variable, and absorption from such supplements in the presence of vitamin D insufficiency may be poor. An approximate starting dose for oral calcium supplementation is 5–20 mg elemental calcium/kg/day, but should be titrated by frequent assessment of serum calcium to avoid hypercalcemia.

Vitamin D and analogues

Vitamin D, or cholecalciferol, is available in liquid or tablet formulations. For nutritional disturbances of vitamin D metabolism, this is the preferred choice of agent for therapy. For patients with other disturbances of vitamin D metabolism, hypoparathyroidism, or renal osteodystrophy, numerous pharmacologic preparations are available that bypass the need for hydroxylation in the kidney. Calcitriol, paricalcitol, and doxercalciferol are available in the United States for such

therapy. Their use should be restricted to a specialist in metabolic bone diseases.

Hypercalcemia

Hypercalcemia is defined when serum calcium values are > 10.6 mg/dl or when the blood ionized calcium is > 1.38 mmol/L. Broadly, hypercalcemia can be divided into disorders of parathyroid function, vitamin D function, or of their receptors. Numerous miscellaneous causes exist as well. Table 3.4 details the causes of hypercalcemia in infants and children.

Table 3.4 Causes of hypercalcemia

Artifactual:
- Increased serum albumin

Hyperparathyroidism:
- Infant of mother with hypoparathyroidism
- Adenoma of parathyroid gland
- Multiple endocrine neoplasia

Heritable disorders:
- Calcium-sensing receptor disorders:
  - Familial hypocalciuric hypercalcemia
  - Neonatal severe hyperparathyroidism (SNHPT)
- Williams syndrome
- Jansen syndrome (a form of a metaphyseal dysplasia)
- Hypophosphatasia

Excess vitamin D:
- Surreptitious or intentional excess vitamin D intake
- Ectopic vitamin D synthesis:
  - Granulomatous disease (sarcoidosis, tuberculosis)
  - Subcutaneous fat necrosis in neonates

Malignancy-associated:
- Paraneoplastic (PTH-rp or $1,25(OH)_2D_3$ excesses)
- Bone metastases with lysis

Drugs:
- Vitamin D intoxication
- Vitamin A intoxication
- Thiazide
- Lithium therapy

Hypercalcemia of unclear pathogenesis:
- Idiopathic infantile hypercalcemia

Miscellaneous causes:
- Immobilization
- Hyperalimentation (with inappropriately high calcium)
- Hypophosphatemia
- Adrenal insufficiency
- Thyrotoxicosis
- Milk-alkali syndrome
- Down syndrome

Clinical manifestations

The symptoms of chronic hypercalcemia include muscle weakness, anorexia, nausea, vomiting, constipation, altered mental status, depression, hypertension, and weight loss. Additionally, polydipsia and polyuria may result from impairment in tubular concentrating ability. Nephrocalcinosis may occur with prolonged hypercalcemia, causing progressive decrease in renal function. Nephrolithiasis may be seen with persistent and long-standing hypercalcemia, and can manifest with flank pain and hematuria. Skeletal involvement (hyperparathyroidism) may lead to fractures. Infants may exhibit poor feeding, failure to thrive, and hypotonia. Some patients, however, may be asymptomatic, presenting only due to incidental laboratory findings of the elevated serum calcium.

Clinical syndromes and conditions

Hyperparathyroidism

Primary hyperparathyroidism is a rare disorder in children. Median age at presentation in a recent study was 16.8 years (range 4–18.9 years).[37] Solitary benign adenomas of the parathyroid gland are the commonest pathology (65–85%) in such patients, whereas diffuse hyperplasia of the glands accounts for the remaining 15–35% of cases.[37–39] Of those with diffuse parathyroid hyperplasia, the disorder can result from multiple endocrine neoplasia (MEN) or familial cases without MEN.

Serum calcium level in primary hyperparathyroidism is often >14 mg/dl and results generally in symptomatic disease. Affected patients have low serum phosphorus as well as hypercalciuria. Renal stones and nephrocalcinosis may be the presenting manifestations in some patients. Skeletal effects of hyperparathyroidism include subperiosteal bone resorption, cyst formation, and 'brown tumors' in severe and long-standing cases. Treatment consists of surgical removal of the parathyroid glands, in an effort to control hypercalcemia and its complications.

Familial hypocalciuric hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is a benign disorder characterized by lifelong hypercalcemia, normal PTH level, and lack of hypercalciuria. The parathyroid glands are normal in histologic structure, and subtotal parathyroidectomy does not cure the disorder.[40] FHH is inherited as an autosomal dominant disorder and results from one of several known mutations in one allele for the gene that encodes the extracellular calcium-sensing receptor in the parathyroid gland and in the kidneys.[41] This leads to the characteristic findings of reduced urine calcium, despite the systemic hypercalcemia. Patients with FHH are asymptomatic, and no treatment is necessary. This disorder is commonly mistaken for primary hyperparathyroidism, and it is important to recognize in order to avoid unnecessary parathyroidectomy.

Neonatal severe hyperparathyroidism

Severe hypercalcemia associated with hyperparathyroidism in neonates is caused by homozygous mutation of the calcium-sensing receptor and is termed neonatal severe hyperparathyroidism (NSHPT).[42] Whereas heterozygous mutation of the calcium-sensing receptor leads to benign familial hypercalcemia, NSHPT is associated with severe life-threatening hypercalcemia in the neonatal period.[43] Clinical manifestations consist of feeding difficulties, respiratory distress, hypotonia, failure to thrive, and unexplained fractures. Radiography of the long bones reveals subperiosteal resorption, demineralization, and fractures. Onset in later childhood, and even in adults, has been reported.[43,44] Emergency parathyroidectomy is generally advocated to control severe hypercalcemia, but a more conservative management with pamidronate has been reported in some cases.[44]

Vitamin D excess states

Vitamin D intoxication is rare but may result from ingestion of milk products fortified with vitamin D, or when excessive vitamin D is used as a supplement in children.[45,46] Other etiologies of vitamin D-mediated hypercalcemia include disorders causing extrarenal or ectopic production of $1,25(OH)_2D$, the active hormone of the vitamin D endocrine system. The latter category includes granulomatous diseases, such as sarcoidosis or tuberculosis, as well as subcutaneous fat necrosis, in which macrophage production of the active vitamin D hormone may occur in an unregulated manner.[47–49]

Humoral hypercalcemia of malignancy

Several mechanisms can cause hypercalcemia associated with malignancies.[50] A humoral factor mimicking the actions of PTH in numerous malignancies had been postulated for over half a century. In 1987, the PTH-related peptide (PTH-rP), a gene product that is separate from PTH and the cause of hypercalcemia, was isolated from carcinoma of lung.[51] PTH-rP shares structural homology with PTH in its amino terminal portion and results in the humoral hypercalcemia of malignancy (HHM).[51,52] PTH-rP has been associated with numerous solid organ and hematologic malignancies.

A second cause of hypercalcemia of malignancy involves ectopic $1,25(OH)_2D_3$ production by the malignant cells.[53,54] Increased intestinal calcium absorption, osteoclastic bone resorption, and decreased renal calcium excretion have been implicated in the pathogenesis of hypercalcemia as a result of ectopic $1,25(OH)_2D_3$ production in malignancies.[50] A third cause of hypercalcemia of malignancy is tumor cell metastasis to bone, producing lytic lesions and resultant hypercalcemia secondary to osteoclastic bone resorption.

Idiopathic hypercalcemia

Williams syndrome is the most well-recognized disorder under the category of idiopathic hypercalcemia. Williams syndrome is characterized by supravalvular aortic stenosis, elfin-like facies, and hypercalcemia. The disorder is caused by a 1.5-Mb deletion containing the elastin gene and flanking genes, on chromosome 7q11.23.[55] Hypercalcemia has been reported in 5–15% of patients with Williams syndrome.[56,57] The mechanism of the hypercalcemia remains obscure, but may involve altered vitamin D metabolism.

Idiopathic infantile hypercalcemia (IIH) is another clinical disorder that shares some phenotypic features with Williams syndrome. Patients with IIH have been found to have an elevated plasma level of PTH-rP.[58] However, since there are several splice variants of PTH-rP in humans, it is unclear that the same molecule that is elevated in HHM is responsible for this disorder too.

Jansen syndrome (metaphyseal dysplasia), which was previously classified as a cartilage dysplasia, is associated with hypercalcemia. Clinically, this disorder is characterized by a rachitic-appearing skeletal structure present from birth. Several mutations in the gene encoding the common PTH/PTH-rP-receptor-1 have been associated with this disorder.[59,60] Hypercalcemia results from ligand-independent, autoactivation of this G-protein-coupled receptor. Despite the findings of biochemical effects of an elevated PTH level, PTH and PTH-rP are undetectable in the circulation in this disorder.

Evaluation of hypercalcemia

Apart from a thorough history and physical examination, evaluation of hypercalcemia should include concurrent measurement of serum phosphorus, an evaluation of acid–base status by serum electrolytes coupled with a pH value (venous blood obtained without a tourniquet is acceptable), serum intact or biointact PTH levels, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, serum magnesium, and evidence of kidney function through a serum creatinine level. Measuring the plasma level of PTH-rP may be necessary in some patients. Urinary excretions of minerals and electrolytes may also be needed in some circumstances. The focus of these investigations is to determine the interplay of hormones controlling the gastrointestinal absorption, skeletal resorption, and renal excretion of calcium. Figure 3.7 provides an algorithm for the diagnostic evaluation of hypercalcemia.

Parathyroid hormone assay

Based on the plasma PTH level, patients with hypercalcemia can be segregated into those with low PTH and those with inappropriately normal or increased levels of PTH. The latter situations are found in primary hyperparathyroidism and in familial hypocalciuric hypercalcemia (FHH).

Vitamin D level

If a suppressed level of PTH is found in the diagnostic work-up of a hypercalcemic patient, the differential diagnosis shifts to diseases associated with elevated circulating vitamin D metabolites. Normal levels of vitamin D metabolites, on the other hand, should prompt investigations of other sources of the hypercalcemia, such as a malignancy. In the later case, measurement of the serum PTH-rP level should be considered.

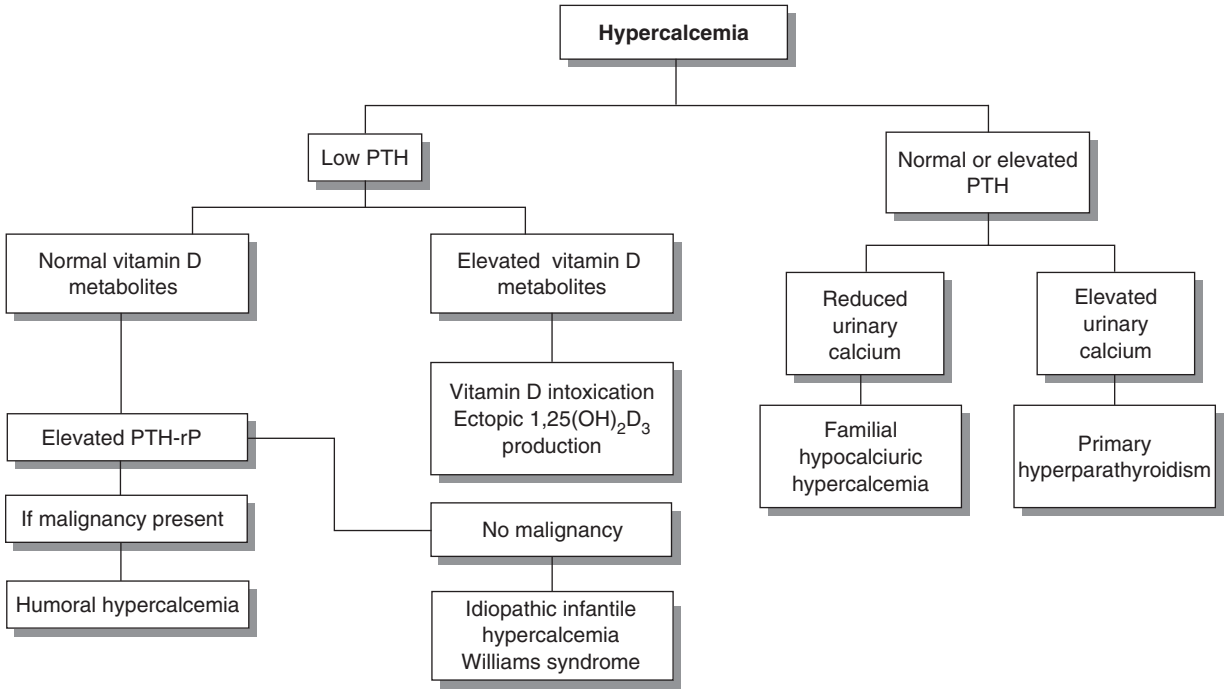

Figure 3.7 A suggested algorithm for evaluation of patients with hypercalcemia. Not all possible etiologies are shown in the algorithm.

Treatment of hypercalcemia

The treatment of hypercalcemia largely depends on the severity of the abnormality and the symptoms. In mild cases, no treatment may be necessary, serum calcium levels should be followed, and all calcium or vitamin D supplementation should be discontinued. Consideration of the use of a calcium-restricted diet may also be appropriate for treatment of mild hypercalcemia. Moderate hypercalcemia (serum calcium 12–14 mg/dl or 3–3.5 mmol/L) should be treated with saline diuresis, and calcitonin may also be considered for refractory cases. Hypercalcemic crises (serum calcium > 14 mg/dl or 3.5 mmol/L) require urgent attention and therapy.

Saline diuresis

With more severe aberrations of serum calcium and/or clinical signs and symptoms referable to it, hydration with saline and the use of furosemide may be required to treat hypercalcemia. Saline diuresis induces hypercalciuria, and furosemide further reduces distal renal tubular calcium reabsorption. Reduction in serum calcium level occurs gradually over several days. Such a therapy should, however, be used with caution in infants and younger children because of the risk of inducing hypernatremia.

Calcitonin

Subcutaneous or intramuscular injection of calcitonin can result in an acute decrease in serum calcium level. Nasal spray of calcitonin is not yet approved for the purposes of treatment of hypercalcemia. The starting dose of calcitonin is 2–4 IU/kg, given every 12 hours, subcutaneously. Gradual resistance to therapy often develops after extended use.

Parathyroidectomy

When the underlying cause of hypercalcemia is primary hyperparathyroidism or uncontrolled tertiary hyperparathyroidism, parathyroidectomy may be indicated to relieve recalcitrant hypercalcemia.

Pamidronate

Although pamidronate use for treatement of hypercalcemia has been reported in neonates and children,[44] data on its long-term safety are unclear. The use of this drug should be restricted to a specialist in metabolic bone diseases.

Other therapies

Treatment of underlying malignancy may be necessary for resolution of hypercalcemia in malignancy-associated hypercalcemia. Other therapeutic agents may include corticosteroids or mithramycin. Caution is urged with the use of these compounds by the general practitioner. Hemodialysis, using a low-calcium dialysate bath, should be considered for patients who are resistant to therapy or have life-threatening severe hypercalcemia.

Magnesium metabolism

Magnesium is a dominant intracellular cation and is essential for metabolic processes. It is also an important part of bones and teeth. Bone and muscle are the major tissue pools for magnesium within the body. Bones account for approximately 60% of the total body magnesium stores, while the remaining 40% of magnesium resides intracellularly in soft tissues, with more than half of this being in muscle cells. Liver is also a prominent store of magnesium.

Renal handling of magnesium

Of the circulating magnesium, approximately 70–80% is ultrafilterable, and 20–30% is protein-bound and non-ultrafilterable. Of the ultrafilterable fraction, 90% is in an ionized form, and the remaining 10% is complexed to citrate, bicarbonate, and phosphate. Of the filtered magnesium, 20% is reabsorbed in the proximal tubule, and most of the remainder (65–70%) is reabsorbed within the thick ascending limb of the loop of Henle (Figure 3.8). The remainder of magnesium reabsorption occurs in the distal convoluted tubule (5–10%). Renal conservation is excellent, and urinary excretion matches net intestinal absorption in normal individuals. Less than 5% of the filtered magnesium normally appears in the final urine.[61]

Magnesium homeostasis

After its absorption from the small intestine, magnesium homeostasis is maintained through its excretion by the kidney. Vitamin D, PTH, and increased sodium absorption in the intestine may directly enhance magnesium absorption. Conversely, calcium, phosphate, and increased intestinal motility decrease absorption of magnesium from the gastrointestinal (GI) tract.[62] A small amount of magnesium is secreted into the GI tract normally, and its excretion is increased in diarrhea.

Both chronic and acute metabolic acidosis increase urinary excretion of magnesium, whereas metabolic alkalosis decreases it. Other factors that cause inhibition of renal magnesium reabsorption include expansion of the extracellular fluid volume, glucagon, calcium, low PTH levels, and diuretics. Loop diuretics such as furosemide inhibit the Na–K–2Cl transporter and diminish the paracellular reabsorption of magnesium by reducing the transepithelial voltage. Thiazide diuretics act primarily at the Na–Cl cotransporter in the distal convoluted tubule and may cause small and variable magnesium wasting. Volume contraction, magnesium deficiency, thyrocalcitonin, and elevated PTH levels enhance renal magnesium reabsorption.[61]

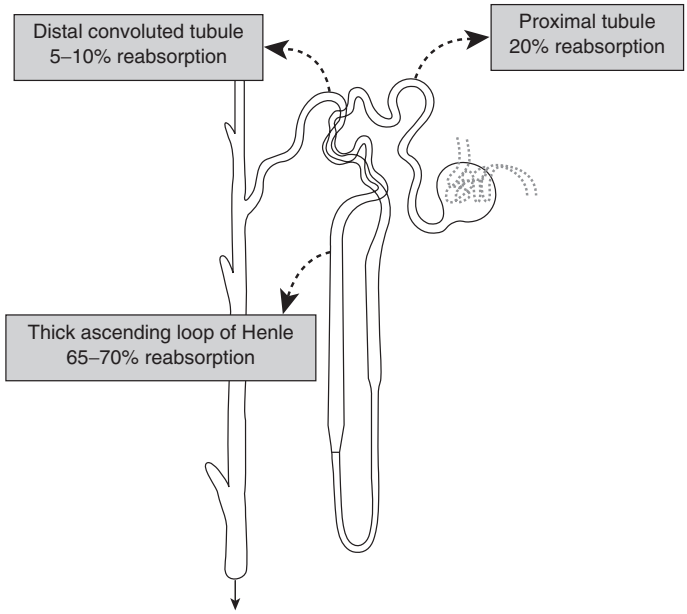

Figure 3.8 Sites of reabsorption of magnesium in the nephron.

Hypomagnesemia

Hypomagnesemia may arise from either diminished intake, or excessive excretion via the kidneys or the GI tract. Inadequate intake of magnesium may result from dietary deficiency, or in patients in whom insufficient amount of magnesium has been provided during prolonged intravenous fluid therapy. Malabsorptive states such as chronic diarrhea or celiac disease may also lead to magnesium deficiency. Excessive urinary excretion of magnesium may result from diuretic therapy, primary aldosteronism, hyperparathyroidism, postobstructive diuresis, acute tubular necrosis, diuresis following renal transplantation, and nephrotoxic agents such as cyclosporine, cisplatinum, aminoglycosides, and amphotericin B. Several inherited disorders characterized by hypomagnesemia have also been identified. Functional deficiency of magnesium may be caused by intracellular shift of magnesium during respiratory alkalosis and treatment of diabetic ketoacidosis with insulin. Postparathyroidectomy 'hungry bone syndrome', as well as refeeding of malnourished children, can also result in hypomagnesemia due to the incorporation of this ion into the regenerating tissues. Table 3.5 lists the causes of hypomagnesemia encountered in children.

Clinical manifestations

The symptoms of hypomagnesemia largely consist of increased neuromuscular irritability, including tremors, seizures, tetany, carpopedal spasms, seizures, and neuropsychiatric manifestations (Table 3.6). Positive Chvostek and Trousseau signs seen in hypocalcemia may also be elicited in patients with hypomagnesemia. Disorientation, nausea, anorexia, abnormal cardiac rhythm, and ECG changes, such as prolonged QT interval, U waves, or non-specific T-wave changes also may occur.[63] Hypocalcemia and hypokalemia are common biochemical findings encountered in hypomagnesemia. It is important to note that the degree of symptoms does not always correlate with the serum level of magnesium, which may be because magnesium is largely an intracellular cation and the serum level may not reflect the reduction in total body magnesium content.

Clinical syndromes and conditions

Gitelman syndrome

Gitelman syndrome is an autosomal recessive disorder characterized by metabolic alkalosis, hypokalemia, hypomagnesemia, and hypocalciuria. Other findings include increased urinary loss of magnesium and potassium.[64–66] Gitelman syndrome results

Table 3.5 Causes of hypomagnesemia

Poor absorption/intake
Protein-calorie malnutrition
Chronic diarrhea
Selective defect of magnesium absorption in the intestine

Magnesium shift into cells
Post-parathyroidectomy hungry bone syndrome
Insulin, in treatment of diabetic ketoacidosis
Respiratory alkalosis
Refeeding in malnutrition

Renal magnesium wasting
Inherited disorders:
- Hypomagnesemia with secondary hypocalcemia
- Isolated familial hypomagnesemia:
  - Autosomal dominant
  - Autosomal recessive
- Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (paracellin-1 mutations)
- Tubular sodium/chloride transport defects:
  - Gitelman syndrome
  - Bartter syndrome

Drug use:
- Aminoglycoside
- Cyclosporine
- Cisplatinum
- Amphotericin B
- Dopamine
- Insulin
- Loop and thiazide diuretics

States of diuresis:
- Postobstructive diuresis
- Acute tubular necrosis – diuretic phase
- Volume expansion
- Osmotic diuresis
- Postrenal transplant diuresis

Miscellaneous disorders:
- Hypoparathyroidism
- Phosphate deprivation
- Hypercalcemia
- Hyperthyroidism

Table 3.6 Manifestations of magnesium depletion

Neuromuscular
Muscle weakness
Positive Chvostek and Trousseau signs
Spontaneous carpopedal spasm
Seizures
Psychosis

Cardiovascular
Prolonged PR interval
Widened QRS complex
Inversion of T waves
Life-threatening ventricular arrhythmias
Enhanced toxicity of cardiac glycosides

Metabolic/blood chemistry
Resistant hypocalcemia
Resistant hypokalemia
Increased insulin secretion
Carbohydrate intolerance

from inactivating mutations in the *SLC12A3* gene (mapped to chromosome 16q) that encodes the thiazide-sensitive Na–Cl cotransporter present in the distal convoluted tubule of the kidney.[66] These patients usually present during childhood or adolescence and exhibit normal linear growth. Although often asymptomatic, transient episodes of weakness and tetany due to profound hypomagnesemia can be observed. Variations in phenotype are common, even within the same family with the identical gene mutation.[67] Adults with Gitelman syndrome can occasionally develop chondrocalcinosis with deposition of calcium pyrophosphate dehydrate crystals.[68]

Bartter syndrome

Bartter syndrome is an autosomal recessive disorder characterized by poor growth, hypokalemia, metabolic alkalosis, hyperreninemia, lack of hypertension, and poor vascular response to aldosterone.[69] Although classic Bartter syndrome is not associated with hypomagnesemia, some genetic (mixed Bartter–Gitelman) variants may be associated with magnesium loss and hypomagnesemia.[70]

Hypomagnesemia with secondary hypocalcemia

Hypomagnesemia with secondary hypocalcemia is an autosomal recessive disorder that presents in the newborn period with seizures, tetany, and muscle spasms. This disorder is believed to result from a primary defect in intestinal magnesium transport.[71] Hypocalcemia results from parathyroid failure as a result of sustained magnesium deficiency. Mutations in a novel gene *TRPM6*, encoding an ion channel expressed throughout the intestinal tract and within distal convoluted tubule cells, have been reported.[72] This disease can be fatal without the administration of high-dose oral magnesium.

Isolated familial hypomagnesemia

Isolated familial renal magnesium wasting is a rare but increasingly recognized disorder. The disorder has been reported as a dominantly or recessively inherited condition. In the isolated dominant hypomagnesemia (IDH), low serum magnesium is seen in conjunction with renal magnesium wasting and hypocalciuria.[73] This disorder is distinguished from Gitelman syndrome by absence of hypokalemic metabolic alkalosis. Patients with IDH can present in the neonatal period and early childhood with severe hypomagnesemia. Mutations in the *FXYD2* gene located on chromosome 11q23 that result in abnormality in

the γ subunit of the basolateral Na^+–K^+-ATPase in the distal convoluted tubule have been proposed to be the abnormality in IDH.[74] Others have reported lack of an *FXYD2* gene mutation, suggesting that IDH may be caused by other genetic mutations.[75] Isolated recessive hypomagnesemia (IRH) also presents in childhood with manifestations of hypomagnesemia, but is not associated with hypocalciuria.[76] No candidate gene for this disorder has yet been identified.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHN) is an autosomal recessive disorder in which nephrocalcinosis is the cardinal finding. The biochemical abnormalities include hypomagnesemia with hypermagnesiuria, and normal serum calcium with hypercalciuria. Some patients may also have findings of partial distal renal tubular acidosis.[77] Patients may present in early childhood with urinary tract infection, nephrolithiasis, polyuria, polydipsia, and failure to thrive. Manifestations of hypomagnesemia such as tetany and seizures are also common. Ocular abnormalities have been reported in these patients, and include myopia, nystagmus, and chorioretinitis.[78] Patients with FHHN eventually progress to chronic renal failure in childhood or adolescence, and this feature distinguishes this disorder from other causes of hypomagnesemia such as Gitelman syndrome or isolated familial hypomagnesemia. Hyperparathyroidism, disproportionate to renal insufficiency, has also been reported, and may be seen before onset of renal dysfunction. Therapy is aimed to reduce the progression of nephrocalcinosis and renal stones with thiazide diuretics. Renal transplantation is curative. Mutations in the gene *CLDN16*, located on chromosome 3q which encodes for paracellin-1, a member of a family of tight junction proteins, have been reported in patients with FHHN.[79]

Autosomal dominant hypoparathyroidism

Autosomal dominant hypoparathyroidism may present in infancy with hypomagnesemia and hypocalcemia, with increased urinary excretion of magnesium and calcium. Defects in the *ECaSR* gene encoding the extracellular calcium/magnesium (Ca^{2+}/ Mg^{2+}) sensing receptor in the parathyroid gland have been implicated in this disorder.[21] An activating mutation in this gene shifts the set point of the receptor and enhances the affinity of the mutant receptor for extracellular calcium and magnesium, thereby diminishing PTH secretion and reducing the renal tubular reabsorption of magnesium and calcium.

Evaluation

A thorough clinical history and examination and evaluation of serum magnesium, calcium, and phosphorus levels should be conducted in patients demonstrating hypomagnesemia. The focus of investigations is to determine whether the hypomagnesemia is the result of nutritional inadequacy, gastrointestinal diseases, or due to excessive renal wasting. Kidney function and measuring urinary calcium and magnesium excretions, preferably in a 24-hour sample, should be conducted. Fractional excretion of magnesium can be determined on a spot sample of urine, using the formula:

$$FE_{Mg}(\%) = \frac{U_{Mg} \times P_{Cr}}{(0.7 \times P_{Mg}) \times U_{Cr}} \times 100$$

where FE_{Mg} is the fractional excretion of magnesium (%), U_{Mg} is the urinary magnesium concentration (mg/dl), P_{Mg} is the plasma magnesium concentration (mg/dl), P_{Cr} is the plasma creatinine concentration (mg/dl), and U_{Cr} is the urine creatinine concentration (mg/dl). Since only 70% of the plasma magnesium is ultrafilterable (not bound to albumin), the plasma magnesium concentration is multiplied by a factor of 0.7.

$FE_{Mg} > 2.0$ in patients with normal renal function is suggestive of renal magnesium wasting. Patients with extrarenal loss of magnesium, such as occurs with diarrhea or other gastrointestinal disorders, have $FE_{Mg} < 1.5$.

Treatment

Serum magnesium may not reflect the true extent of total body or cellular magnesium deficiency, especially in patients with history of chronic renal or gastrointestinal loss of the ion. An estimation of total body deficit of magnesium under these circumstances is difficult. Mild hypomagnesemia may be treated by increasing dietary intake of magnesium, but symptomatic hypomagnesemia requires oral or intravenous supplementation. The magnesium salts available for clinical use are listed in Table 3.7. Diarrhea is a common side effect of oral magnesium supplementation. Bioavailability and gastrointestinal magnesium absorption of these supplements is highly variable.[80] Magnesium oxide (MagOx) has a higher magnesium content, but its absorption may be less effective than magnesium chloride, or magnesium lactate.[81] Intravenous magnesium therapy is necessary in symptomatic patients, or those with serum magnesium < 0.5 mg/dl. One gram of magnesium sulfate provides approximately 100 mg or 8 mEq of elemental magnesium. Magnesium sulfate (100 mg/ml) in a dose of 25–50 mg/kg/dose can be used as an intravenous infusion over 1–2 hours to correct severe hypomagnesemia with careful cardicic monitoring.

Hypermagnesemia

Because of excellent renal modulation of magnesium homeostasis, hypermagnesemia rarely occurs in patients with normal renal function, except from an accidental toxic ingestion. Hypermagnesemia is defined as a serum magnesium level > 2.5 mEq/L. Sources of magnesium load that may precipitate elevated serum magnesium levels include laxatives (milk of magnesia), enemas, antacids, intravenous fluids with high magnesium load, accidental overdose with magnesium therapy, and neonates born to mothers treated with magnesium sulfate for pre-eclampsia.

Table 3.7 Magnesium content and percentage of elemental magnesium per gram of various salts of magnesium available commercially

Magnesium salt	Brand names	Magnesium (mg/g)	Percent elemental magnesium	Remarks
Magnesium oxide	MagOx; many other brands	603	60.3	Magnesium supplement
Magnesium hydroxide	Milk of Magnesia (MOM); other brands	417	41.7	Used as antacid
Magnesium citrate	Citroma; other brands	162	16.2	Used as bowel cleanser
Magnesium chloride	SlowMag; other brands	120	12.0	Magnesium supplement
Magnesium lactate	MagTab; other brands	120	12.0	Magnesium supplement
Magnesium sulfate	Numerous brands	99	9.9	Bowel cleanser; magnesium supplement. Also available as a parenteral preparation
Magnesium aspartate	Numerous brands	75	7.5	Nutrional supplement
Magnesium gluconate	Numerous brands	54	5.4	Nutritional supplement

Some data in the table obtained from Blaine Pharmaceuticals, Fort Wright, KY. http://www.magox.com/healthcaretypes.htm

Addison disease may be associated with mildly elevated serum magnesium. A rare syndrome of decreased renal magnesium excretion and hypermagnesemia has also been reported.[82]

Symptoms of hypermagnesemia include hyporeflexia, flaccidity, respiratory depression, hypotension, disturbances in cardiac atrioventricular (AV) conduction, drowsiness, and coma. In addition to careful history-taking to elucidate an etiology, the evaluation should include serum and urinary measurements of calcium and magnesium. Treatment of hypermagnesemia includes intravenous calcium gluconate, exchange transfusion, and diuresis. Dialysis may be necessary for patients with renal failure and severe hyper magnesemia.

Phosphorus metabolism

Phosphorus is mainly stored in the body within the skeleton and teeth. Besides being a vital constituent of bone mineral, phosphorus is also required for vital intracellular metabolic processes, such as energy metabolism, protein phosphorylation, and nucleotide and phospholipid metabolism. Phosphorus, as phospholipids, is an important component of cell membranes. Of the total body phosphorus, about 85% resides in the skeletal stores, and the remaining 15% is present in the soft tissues as an intracellular ion. A small fraction of the total phosphorus is found in the extracellular fluid. Within the plasma, phosphorus is present as organic compounds (phospholipids and phosphate esters), inorganic phosphates (as HPO_4^{2-} or $H_2PO_4^-$) and as complexes with other ions, such as calcium and magnesium ions. About 10–15% of plasma inorganic phosphorus is protein-bound and the remaining 85–90% is ultrafilterable by the glomeruli. Whereas the adult phosphorus balance is zero, growing children have a positive phosphorus balance in order to meet the needs of skeletal growth.[1]

Serum phosphorus is governed by a circadian rhythm, with a rapid decrease in levels early in the morning, a nadir before noon, and a peak after midnight. When measuring the serum phosphorus level, it is best to obtain a specimen in the morning fasting state to minimize the effect of dietary changes on the serum level. The normal serum concentration of phosphorus varies with age, with values being higher in infants than in older children and adults (Table 3.8). Other factors that may affect the serum phosphorus level include metabolic acidosis and intravenous calcium infusion, both of which may increase the serum phosphorus. Decreased serum phosphorus level may result from intravenous infusion of glucose or insulin, acute respiratory alkalosis, and epinephrine administration.

Table 3.8 Serum phosphorus level in normal infants and children

Age group	Serum phosphorus level (mg/dl)
Infants	4.8–7.4
Toddlers	4.5–5.8
Mid-childhood	3.5–5.5
Adolescence to adulthood	2.4–4.5

Renal handling of phosphorus

Between 80 and 97% of the filtered phosphorus is reabsorbed by the renal tubules, mostly by the proximal tubules (70–80%), 5–10% in the distal tubule, and 2–3% in the collecting tubule (Figure 3.9). In the proximal tubule, phosphorus transport is coupled to sodium transport, being unidirectional, against a gradient, and as a transcellular, secondary active process. Proximal tubular transport of phosphate is mediated by the sodium–phosphate ($Na–P_i$) cotransporter present in the apical brush-border membrane. Three distinct types of $Na–P_i$ cotransporters – type I, type II, and type III – have been described in the renal tubules. Of these, type IIa $Na–P_i$ cotransporter is believed to be the most significant phosphate reabsorption protein. The $Na–P_i$ cotransporter picks 1 phosphate ion along with 3 sodium ions and delivers these into the proximal tubular cells. Phosphorus exits the tubular cell by the active basolateral Na–K-ATPase pump.[83,84]

Phosphorus homeostasis

In adults, dietary intake results in a net intestinal absorption of 60–65% of the ingested quantity of phosphorus. In infants, this net absorption is higher and may exceed 90%. Most of the ingested phosphorus is absorbed from the duodenum and jejunum, through passive diffusion via a paracellular pathway. When the lumenal concentration is low, phosphorus may also be absorbed actively via a sodium-dependent transcellular process. Once in the extracellular fluid compartment, phosphorus exists in equilibrium with the bone and soft-tissue pools.

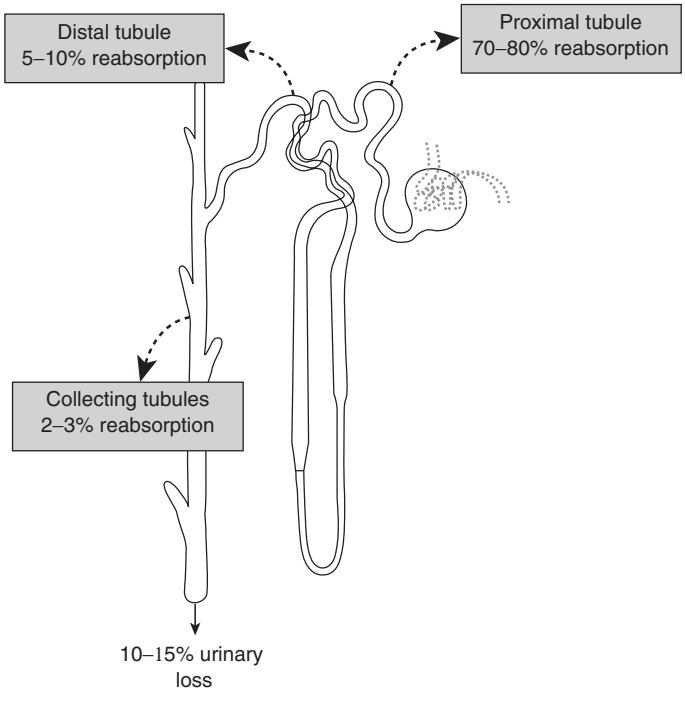

Figure 3.9 Sites of reabsorption of phosphorus in the nephron.

Vitamin D

Vitamin D plays an active role in phosphorus homeostasis. Hypophosphatemia increases renal $1,25(OH)_2D_3$ synthesis.[85,86] This leads to increased phosphorus and calcium absorption from the gut, and increased mobilization of calcium and phosphorus from bone. These combined effects lead to an increase in serum calcium and phosphorus. Elevated serum calcium by causing a decrease in PTH secretion, enhances renal phosphorus reabsorption and increases renal calcium excretion. Hypophosphatemia directly increases calcium excretion in the kidney. The net result of all of these factors is an increase in serum phosphorus concentration, with relatively little change in the serum calcium. Hyperphosphatemia results in opposite effects by decreasing levels of $1,25(OH)_2D$ and increasing PTH levels, thereby decreasing the serum phosphorus level.[85,86]

Parathyroid hormone

PTH inhibits phosphate reabsorption in the proximal tubule by inhibiting phosphate transport and reducing the number of type IIa $Na–P_i$ cotransporters in the membrane. In contrast, absence of PTH (e.g. after parathyroidectomy) increases the number of active $Na–P_i$ cotransporters.[83]

Phosphatonin(s)

Investigations of patients with inherited disorders of phosphate metabolism have pointed to the possible existence of a phosphaturic hormone(s), distinct from PTH, known by the term phosphatonin. A number of candidates for phosphatonin(s) have been suggested over the last decade. Whereas the fibroblast growth factor-23 (FGF-23) is considered to be the chief contender for phosphatonin, other agents being considered are secreted frizzled-related protein-4 (sFRP-4), matrix extracellular phosphoglycoprotein, and FGF-7.[87] Evidence to date suggests that FGF-23 is derived mostly from the bone,[88] and parathyroid gland appears to be an unlikely synthetic site.[89] More work is needed to define the role of phosphatonin(s) in health and control of phosphorus balance.

Other regulators of phosphate

Independent of PTH, growth hormone increases phosphate reabsorption in the kidney by its effector protein, IGF-1 the $Na–P_i$ cotransporter in the proximal tubule. Other factors that decrease renal phosphorus excretion include dietary restriction of phosphorus, alkalosis, thyroid hormone, and insulin.[83] Factors that may increase renal phosphorus excretion are volume expansion, acidosis, long-term vitamin D use, calcitonin, mannitol, loop diuretics, thiazides, glucose, glucocorticoids and growth for deficiency.[83]

Hypophosphatemia

Age-specific normal values for serum phosphorus are shown in Table 3.8 and serum concentration less than age-appropriate ranges indicate hypophosphatemia. It is important to note that serum phosphorus may not reflect a true total body phosphorus

deficit, since it is largely an intracellular ion. Both primary and secondary hyperparathyroidism may result in phosphaturia and consequent hypophosphatemia. Non-selective urinary phosphate wasting, leading to hypophosphatemia, can be seen in numerous renal diseases, such as Fanconi syndrome, distal renal tubular acidosis, postobstructive diuresis, and the diuretic phase of acute tubular necrosis.

Hypophosphatemia with reduced urinary phosphorus excretion may result from nutritional deficiency of phosphorus, malnutrition, or impaired intestinal absorption due to phosphorus-binding antacids or intestinal disorders. Refeeding with a large carbohydrate load after prolonged malnutrition or during a leukemic blast crisis, where phosphate is incorporated in the proliferating cells, can lead to hypophosphatemia. Respiratory alkalosis stimulates the formation of intracellular sugar–phosphate moieties and may cause hypophosphatemia with low urinary phosphorus. Intracellular phosphorus shift may also result from infusion of glucose, fructose, lactate and amino acid infusions, exogenous administration of insulin, glucagon, androgens, and β-agonists. Table 3.9 lists the causes of hypophosphatemia seen commonly in infants and children.

Table 3.9 Causes of hypophosphatemia

Poor phosphate intake/absorption
Malnutrition
Anorexia nervosa
Phosphate-binding antacids (e.g. calcium carbonate – Tums)
Malabsorption
Inadequate phosphate in intravenous hyperalimentation

Shift of phosphate into cells
Rapid infusion of large dose of carbohydrates (glucose, fructose)

Endogenous or exogenous hormones:
- Insulin for correction of hyperglycemia
- Catecholamines – epinephrine, dopamine, albuterol
- Glucagon
- Calcitonin

Respiratory alkalosis

Cellular incorporation of phosphate:
- Post-parathyroidectomy hungry bone syndrome
- Leukemic blast crises
- Refeeding in malnutrition

Renal phosphate wasting (phosphaturia)
Proximal renal tubular acidosis (Fanconi syndrome)
Primary hyperparathyroidism
Metabolic acidosis
Diuretic therapy
Glucocorticoid therapy
Mineralocorticoid therapy
Volume expansion
Sodium bicarbonate infusion

Inherited disorders
PHEX mutations:
- X-linked hypophosphatemic rickets

FGF-23 mutation:
- Autosomal dominant hypophosphatemia

Unclear genetic defect:
- Hereditary hypophosphatemia with hypercalciuria

Miscellanous disorders
Postrenal transplant hypophosphatemia
Continuous renal replacement therapy – inadequate phosphorus dialysate
Acute systemic infections

Clinical manifestations

Systemic symptoms of low serum phosphorus generally result from decreased intracellular ATP levels and impaired tissue oxygen delivery, especially in hypophosphatemia of long-standing duration. Symptoms may include anorexia, vomiting, paresthesias, myopathy, confusion, and seizures (Table 3.10). Life-threatening events, such as cardiac failure, ventricular arrhythmias, hypotension, rhabdomyolysis, respiratory failure, and coma may result from severe phosphorus deficits.[90] The bony lesion is rickets.

Clinical syndromes and conditions

X-linked hypophosphatemic rickets

X-linked hypophosphatemic rickets (XLH), also known as familial hypophosphatemic rickets, is characterized by growth retardation, clinical rickets, renal phosphate wasting, and hypophosphatemia. Serum calcium and PTH levels are normal, but the $1,25(OH)_2D$ level is low. The disorder is transmitted as an X-linked dominant disease. Mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) have been found to be present in the majority of affected individuals.[91–93] This mutation is believed to prevent inactivation of FGF-23, a phosphaturic factor. Resultant increased FGF-23 concentration causes phosphaturia and the manifestations of XLH (Figure 3.10). Treatment of XLH includes phosphate and calcitriol supplementation. Improvements in growth have been noted with such a therapy, but nephrocalcinosis can also result.[94]

Autosomal dominant hypophosphatemia

Autosomal dominant hypophosphatemia (ADH) is phenotypically a heterogenous disorder. Patients can present either in early childhood (1–3 years) or in the adolescent–adult age groups.[95,96] Clinical manifestations of children with ADH include muscle weakness, short stature, clinical rickets, and bone pain. Adults presenting with this disorder do not have any skeletal deformities, but may have short stature, bone pain, fatigue, and pseudofractures or stress fractures may be seen on radiographs.[96] In women, the disease may first manifest during or after pregnancy. Regression and resolution of hypophosphatemia in the affected individuals has been reported. Serum calcium level is normal, PTH is normal or marginally elevated, and the $1,25(OH)_2D$ level is normal or modestly low. Mutations

Table 3.10 Clinical and laboratory manifestations of phosphate depletion

Muscular
Proximal myopathy
Weakness
Rhabdomyolysis

Gastrointestinal
Dysphagia
Ileus

Respiratory
Hyperventilation
Hypoventilation
Respiratory muscle paralysis

Hematologic
Hemolysis
Impaired phagocytosis
Impaired platelet function, thrombocytopenia

Renal
Magnesuria
Hypercalciuria
Increased tubular phosphate reabsorption
Increased $1,25(OH)_2D_3$ synthesis

Skeletal
Bone pain
Rickets/osteomalacia
Pseudofractures/fractures

Neurologic
Irritability
Confusion
Encephalopathy, coma

in the *FGF-23* gene lead to the formation of a mutant FGF-23 molecule that is resistant to normal cleavage, and its accumulation, is proposed to be the underlying mechanism of phosphaturia and hypophosphatemia (see Figure 3.10).[97,98]

Oncogenic osteomalacia

Tumor-induced osteomalacia (TIO) is a paraneoplastic disorder that is characterized by phosphaturia, hypophosphatemia, and inappropriately low serum levels of 1,25-dihydroxyvitamin D_3. Patients manifest severe bone pain and skeletal demineralization.[99] A variety of tumors are known to cause TIO. Excessive production of FGF-23 or other phosphatanins by the tumors is causative of phosphaturia and consequent hypophosphatemia.[100] Excision of the tumor is curative.

Hereditary hypophosphatemia with hypercalciuria

Hereditary hypophosphatemia with hypercalciuria (HHH) is another disorder of selective renal phosphorus wasting.[101] Clinical manifestations of HHH include short stature, phosphaturia, hypophosphatemia, hypercalciuria, nephrolithiasis, and rickets. The serum $1,25(OH)_2D$ level is elevated, while the PTH level is suppressed. No putative disease-causing mutation has been found. This disorder also does not appear to be caused by a gene mutation of the type II Na–Pi cotransporter.[102] Treatment with phosphorus supplementation improves rickets, despite continued phosphaturia.

Hypophosphatemia after renal transplantation

Hypophosphatemia that can persist for up to several months is commonly seen after renal transplantation. Hyperparathyroidism associated with chronic kidney disease persisting in the early course of transplantation has been considered the most likely suspect in the causation of phosphaturia and hypophosphatemia in these patients. The role of a circulating phosphaturic factor in these patients has also been proposed recently.[103] Treatment consists of phosphate supplementation and providing adequate doses of vitamin D.

Idiopathic hypercalciuria

Renal phosphate wasting and hypophosphatemia has been reported in a small group of children with idiopathic hypercalciuria.[104] Vitamin D levels are elevated in these patients and phosphorus supplementation reduces calciuria and restores normal serum phosphorus values.

Hungry bone syndrome

Hungry bone syndrome due to increased avidity of bone for calcium and phosphorus refers to the transient phenomenon of hypocalcemia and hypophosphatemia seen after the resolution of long-standing primary or secondary hyperparathyroidism.[105] This disorder is commonly seen following parathyroidectomy in patients with primary or secondary hyperparathyroidism. Manifestations of hypophosphatemia as well as hypocalcemia can persist from weeks to several months. Oral supplemental calcium and vitamin D therapy is needed for treatment of most patients with hungry bone syndrome. An occasional patient may require prolonged intravenous calcium supplementation and vitamin D to avoid life-threatening hypocalcemia. Hypophosphatemia is usually responsive to oral supplementation.

Evaluation

Disorders of hypophosphatemia can be classified as those with elevated urinary phosphorus and those with reduced urinary phosphorus. If the urinary phosphorus level is elevated, this suggests a phosphaturic mechanism, and serum PTH measurement is essential. An elevated PTH points to disorders of hyperparathyroidism – primary or secondary. If the serum PTH level is normal or low, then it is necessary to determine whether the urinary losses are selective for phosphorus or whether there is non-selective phosphorus wasting, as discussed above.

Urinary phosphorus excretion and tubular reabsorption of phosphorus can be studied by fractional excretion of phosphorus, using the formula:

$$FE_{PO_4}(\%) = \frac{U_{Phos} \times P_{Cr}}{P_{Phos} \times U_{Cr}} \times 100$$

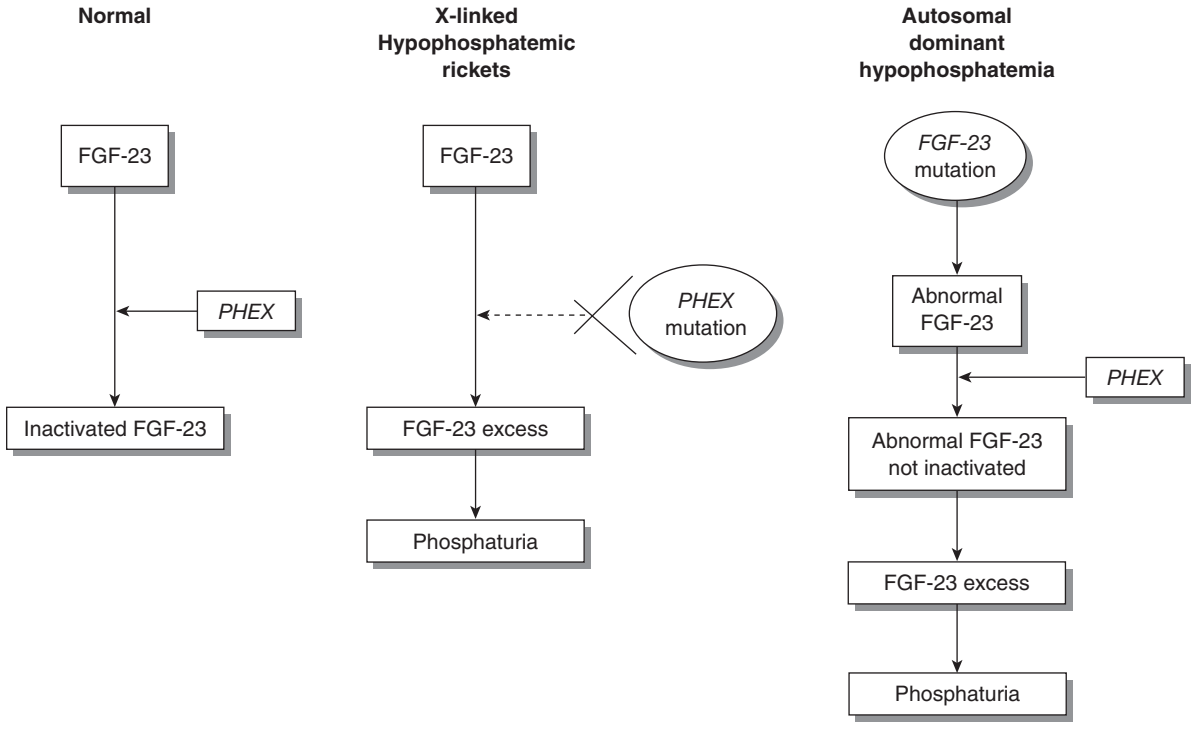

Figure 3.10 Proposed pathogenesis of hypophosphatemia in X-linked hypophosphatemic rickets and autosomal dominant hypophosphatemia. FGF-23, fibroblast growth factor–23; *PHEX*, phosphate-regulating gene with homologies to endopeptidases on the X chromosome.

where FE_{PO4} is the fractional excretion of phosphate (%), U_{Phos} is the urine phosphorus (mg/dl), P_{Phos} is the plasma phosphorus (mg/dl), P_{Cr} is the plasma creatinine (mg/dl), and U_{Cr} is the urine creatinine (mg/dl).

FE_{PO4} in normal children is 15–20%, being lower in growing infants. In the setting of hypophosphatemia FE_{PO4} of >20% indicates phosphaturia. Another derived index of phosphate excretion is tubular reabsorption of phosphate (TRP). TRP represents the percentage of the filtered phosphate that is reabsorbed in the renal tubules, and is derived by the formula:

$$\text{TRP}\ (\%) = 100 - \text{FE}_{\text{PO}_4}$$

Renal tubules reabsorb greater than 80% of filtered phosphate and TRP is >80% in normal children. Higher values of TRP are expected in infants and growing children with high phosphorus accrual rates.

Both FE_{PO4} and TRP can be affected by renal function and plasma phosphorus concentration. Another index considered to be independent of renal function is the ratio of the tubular maximum rate of phosphate reabsorption (TmP) to the glomerular filtration rate (GFR). This index can be calculated either from a nomogram,[106] or may be derived from the formula:

$$\text{TmP/GFR(mg/dl)} = \text{P}_{\text{Phos}} - \frac{\text{U}_{\text{Cr}}}{\text{U}_{\text{Phos}} \times \text{P}_{\text{Cr}}}$$

where U_{Cr} is the urine creatinine (mg/dl), U_{Phos} is the urine phosphorus (mg/dl), P_{Phos} is the plasma phosphorus concentration (mg/dl), and P_{Cr} is the plasma creatinine (mg/dl).

TmP/GFR in normal individuals is 2.8–4.4 mg/dl. Lower TmP/GFR reflects poor tubular phosphate reabsorption (phosphaturia). Tests of tubular phosphate reabsorption can be done on a spot sample of urine, but a short timed collection (2–4 hours) done in a fasting state is usually preferred in order to avoid variability due to dietary intake. A suggested algorithm for diagnosis of hypophosphatemia is given in Figure 3.11.

Treatment

Treatment of hypophosphatemia in patients believed to have a normal total body phosphorus may be deferred, unless clinical symptoms are present. Mild hypophosphatemia (>2.5 mg/dl) may be treated with increased phosphate content in diet. Milk and milk products are particularly high in phosphorus content, and their intake may be encouraged in such patients. Asymptomatic patients with moderate hypophosphatemia (1.5–2.5 mg/dl) may be treated with oral phosphorus supplementation (Table 3.11). Care should be taken not to provide calcium supplementation with meals, since this may further exacerbate hypophosphatemia through binding of dietary phosphorus with calcium, and thereby preventing its absorption.

Intravenous phosphorus infusion therapy is generally reserved for those with symptomatic hypophosphatemia or serum

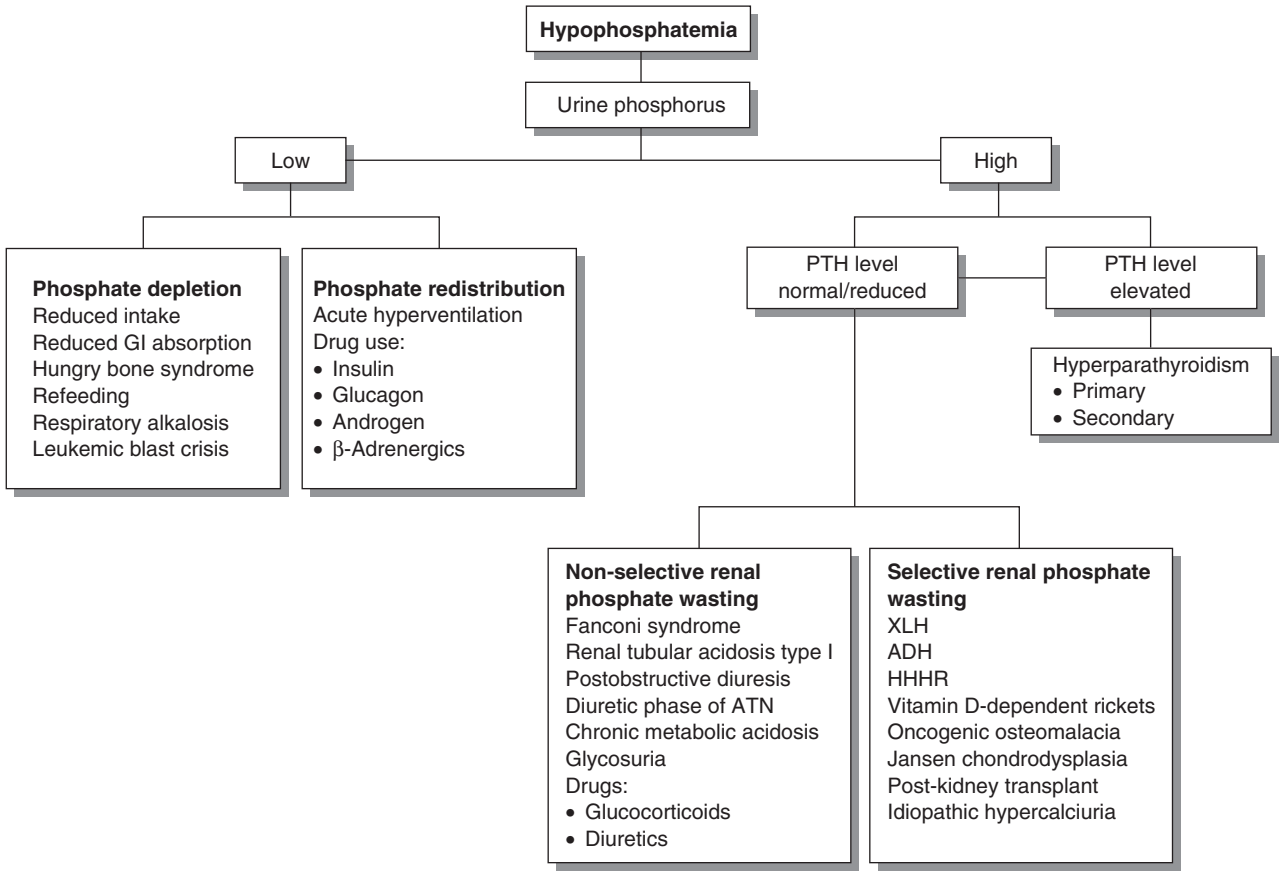

Figure 3.11 A suggested algorithm for evaluation of hypophosphatemia in children. XLH, X-linked hypophosphatemic rickets; ADH, autosomal dominant hypophosphatemia; HHHR, hereditary hypophosphatemia with hypercalciuria and rickets.

Table 3.11 Available preparations of phosphorus for treatment of hypophosphatemia

Formulation	Phosphate content	Sodium load	Potassium load
Oral preparations			
Neutra-Phos	250 mg/pack	7.1 mmol/pack	7.1 mmol/pack
Neutra-Phos K	250 mg/capsule	0	14.25 mmol/pack
K-Phos Original	150 mg/capsule	0	3.65 mmol/capsule
K-Phos Neutral	250 mg/tablet	13 mmol/tablet	1.1 mmol/tablet
Intravenous preparations			
Sodium phosphate	3.0 mmol/ml	4.0 mmol/ml	0
Potassium phosphate	3.0 mmol/ml	0	4.4 mmol/ml

phosphorus level < 1 mg/dl. Sodium phosphate (phosphorus 3.0 mmol/ml and sodium 4.0 mmol/ml) or potassium phosphate (phosphorus 3.0 mmol/ml and potassium 4.4 mmol/ml) can be used for intravenous phosphate replacement. It is important to remember that for every 1 mmol of phosphorus ordered as potassium phosphate, the patient will also receive 1.47 mmol of potassium. The usual dose for elemental phosphate for intravenous use is 0.08–0.16 mmol/kg.[107] The phosphate infusions are formulated in normal saline or dextrose-containing solutions and may be incorporated in the intravenous hyperalimentation. However, these infusions should not be mixed with calcium-containing solutions such as Ringer's lactate, because of the risk of precipitation. Intravenous phosphate replacement is infused over 4–6 hours and the generally recommended rate of infusion is no more than 0.2 mmol/kg/h of elemental phosphorus. Hypocalcemia, hypomagnesemia, and

Table 3.12 Causes of hyperphosphatemia

Artifactual
In-vitro hemolysis of blood samples
Hypertriglyceridemia

Increased intake
Phosphate-containing enemas
Increased phosphate in intravenous nutrition
Cows' milk feeding of premature infants
Excess vitamin D intake (especially in renal insufficiency)
Bisphosphonate therapy

Endogenously increased phosphate load
Tumor lysis
Malignant hyperthermia
Rhabdomyolysis
Hemolysis

Extracellular shift of phosphorus
Acidosis:
- Metabolic acidosis
- Respiratory acidosis

Impaired renal excretion
Acute renal failure
Chronic renal failure
Hypomagnesemia
Endocrinopathies:
- Hypoparathyroidism
- Acromegaly
- Hypothyroidism

Tumoral calcinosis
Hyperostosis

hyperphosphatemia can result following intravenous infusion of phosphate, and patients need close monitoring for these electrolyte abnormalities. Hyperkalemia and consequent cardiac toxicity can result from potassium phosphate infusion, even in patients with normal renal function. Rapid infusions may result in phosphaturia.[108]

Hyperphosphatemia

Values exceeding the normal serum levels of phosphorus for age, as presented in Table 3.8, are termed hyperphosphatemia. Hyperphosphatemia is an uncommon disorder, except in patients with renal disease. Common causes of hyperphosphatemia in children are listed in Table 3.12.

Clinical manifestations

Patients with elevated serum phosphorus levels are frequently asymptomatic. Acute elevations in phosphorus may cause reductions in serum calcium level, and symptoms of hypocalcemia such as paresthesias, tetany, seizures, or cardiac arrhythmias may develop. Hypocalcemia is believed to result from precipitation of phosphorus and calcium in the soft tissues, especially when the calcium × phosphorus product is greater than 70. Symptoms may result from metastatic tissue calcification and calciphylaxis syndrome characterized by rapid calcification in subcutaneous fat and small blood vessels, leading to painful necrosis of affected areas.

Clinical syndromes and conditions

Kidney disease

Hyperphosphatemia is common in acute renal failure (ARF), as well as in chronic kidney disease (CKD). This is especially true if the GFR is below 20 ml/min/1.73 m^2. Despite enhanced phosphate excretion by the surviving nephrons, absolute excretion falls despite elevated PTH level. Hyperphosphatemia is worsened by enhanced dietary phosphorus intake. Whereas hyperphosphatemia is common in the oliguric phase of ARF, hypophosphatemia may be encountered in the diuretic phase or during the oliguric phase.

Cytolytic disorders (tumor lysis)

Hyperphosphatemia is caused by a rapid release of intracellular phosphate during cellular breakdown; potassium and magnesium levels are also increased as a result of intracellular release. This is seen in tumor lysis syndrome, rhabdomyolysis, and severe hemolytic anemia. Underlying kidney dysfunction must also be present, since the normal kidney is able to excrete large quantities of phosphorus.

Tumoral calcinosis

This disorder results from an inability to excrete phosphorus, with resultant hyperphosphatemia and widespread ectopic calcifications. The clinical manifestations include periarticular calcifications located along the extensor surfaces of major joints. Some cases may be associated with nephrolithiasis and dental abnormalities. Serum calcium is normal, and there is inappropriate lack of suppression of $1,25(OH)_2D$. Etiology of this disorder remains unknown, but the role of FGF-23 in this disorder has been recently proposed.[109] Mutations in the *FGF-23* gene are proposed to result in impaired action of FGF-23 in the renal tubules, resulting in enhanced renal phosphate reabsorption and hyperphosphatemia. Some patients respond to the use of calcitonin, phosphate-binding antacids, and reduction in dietary calcium and phosphorus.

Evaluation

The evaluation of hyperphosphatemia should begin by evaluating urinary phosphorus levels (Figure 3.12). If urinary phosphorus excretion is normal or elevated, hyperphosphatemia may either be the result of cellular redistribution of the ion, or from increased phosphorus load from exogenous or endogenous sources. Increased gastrointestinal absorption may result from acute overload of phosphorus, such as after hypertonic sodium phosphate enemas used for preparation of the gastrointestinal tract for surgery, or for treatment of severe constipation.

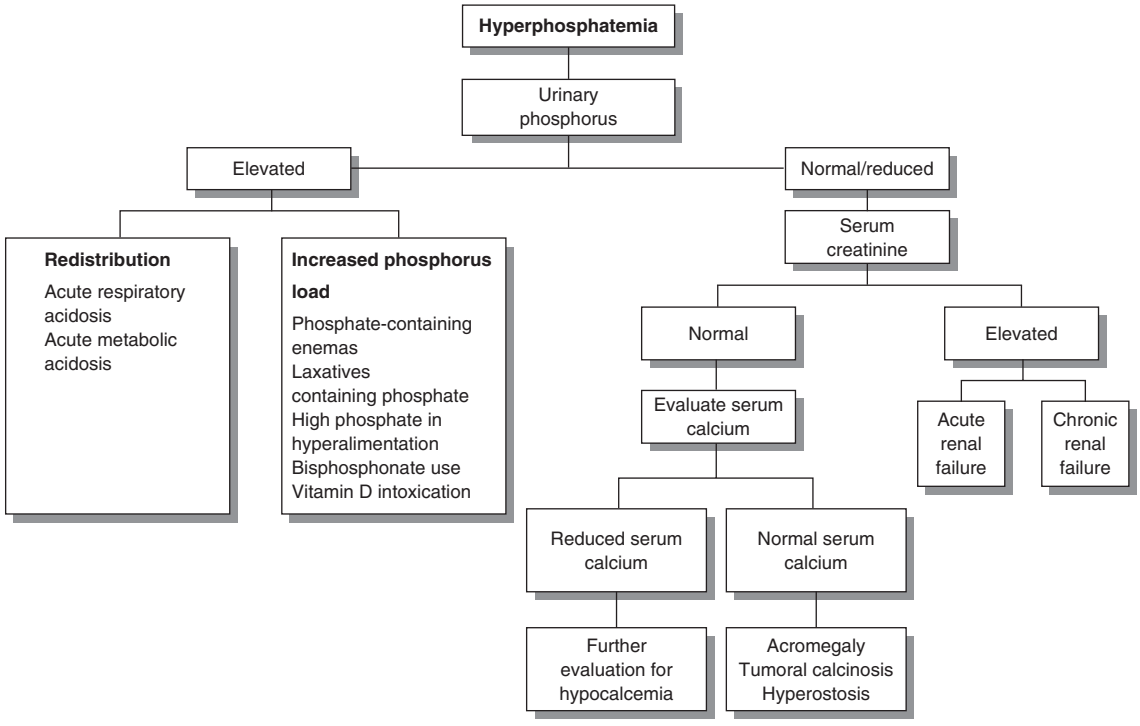

Figure 3.12 A suggested algorithm for evaluation of hyperphosphatemia in children.

Inappropriate dosing of phosphorus infusions for treatment of hypophosphatemia, or in intravenous hyperalimentation, can also lead to hyperphosphatemia, which is associated with increased urinary phosphate excretion. Redistribution of intracellular phosphorus into the extracellular space may occur during both acute respiratory and metabolic acidosis, thereby causing hyperphosphatemia. In addition, bisphosphonate treatment for osteopenia and vitamin D intoxication may both produce hyperphosphatemia with phosphaturia. Decreased urinary phosphate excretion denotes either renal impairment or other disorders (e.g. hypoparathyroidism) that are associated with increased renal tubular reabsorption of phosphorus.

The next investigative step of hyperphosphatemia is determination of renal function and serum calcium. Abnormalities in renal function may denote ARF or CKD, which can be further evaluated by appropriate tests for renal disease. If the serum creatinine is normal, then determining serum calcium is the next diagnostic aid. For disorders associated with low plasma calcium, serum PTH measurement is essential in order to rule out hypoparathyroidism. In the setting of normal serum calcium, mild hyperphosphatemia may be encountered in acromegaly and thyrotoxicosis. Therefore, in addition to a thorough clinical evaluation, growth hormone and thyroid function tests are essential.

Treatment

Treatment of hyperphosphatemia is directed towards managing the underlying etiology. Oral calcium salts may assist in binding dietary phosphorus and prevent phosphorus absorption, and thereby lessen hyperphosphatemia. With severely impaired kidney function, dialysis may be the only feasible treatment, but efficiency of hemodialysis as well as peritoneal dialysis in removal of phosphorus is modest, at best. Continuous renal replacement therapy (CRRT) with dialysis is able to remove phosphorus efficiently, and may be useful in acutely sick patients, such as those with tumor lysis syndrome or acute phosphorus intoxication. It is important to note that CRRT may also remove the therapeutically essential chemotherapeutic agents from these patients undergoing treatment for malignancy.

Concluding remarks

The metabolism of calcium, phosphorus, and magnesium is interdependent and interrelated. The kidney plays an important role in maintaining the homeostasis of all three ions. Advancements in our understanding of the hormonal control, cellular actions, and molecular mechanisms of their handling by the kidneys have resulted in a better understanding of many enigmatic clinical disorders (e.g. hypophosphatemic rickets), and development of newer therapies (e.g. calcitriol). Phosphatonins, a unique new set of hormones that impact phosphate balance through their phosphaturic action on the kidney, still represent an evolving discovery that is beginning to have a profound impact on the pathogenesis of numerous disorders affecting the metabolism of phosphorus. Indeed, these findings may have significant pharmacotherapeutic applications in the years to come, as will selective ability to modulate vitamin D actions in target cells.

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Part II

Epidemiology and evaluation of renal disease

4 Epidemiology of renal disease in children

Craig S Wong and Susan Furth

The increasing incidence and prevalence of end-stage renal disease (ESRD), associated with poor outcomes and high cost, has led to increased awareness of chronic kidney disease (CKD) as an urgent public health problem. By 2010, it is estimated that 650 000 persons in the USA will have ESRD. Medicare costs for these patients will exceed $28 billion per year.

ESRD, the point at which dialysis or kidney transplantation is necessary to ameliorate the physiologic complications of uremia due to kidney failure, represents the most severe stage of CKD. Despite advances in dialysis and transplantation in both children and adults, the prognosis for those with permanent kidney failure is poor, with a significantly higher risk for death in both children and adults with ESRD compared with the general population.[1,2] Many recent epidemiologic studies have demonstrated effective strategies for slowing decline in kidney function, treating complications, and improving outcomes. Therefore, identification of individuals affected by early stages of CKD has become an important goal for the National Institutes of Health (NIH) through the National Kidney Disease Education Project.

The goals of this chapter are to provide an understanding of the magnitude of the public health problem of CKD, to review the stages of CKD, the epidemiology of CKD in the pediatric population, and to discuss the future needs to study CKD in children and the role of the NIH in fostering collaborative studies.

Chronic kidney disease staging

In 2000, the National Kidney Foundation (NKF) Kidney Disease Outcome Initiative (K/DOQI) approved the development of clinical practice guidelines to define CKD and to classify stages in the progression of CKD (Table 4.1). The staging of CKD relies on the level of glomerular filtration rate (GFR) as the index of global kidney function. This effort has provided a broad conceptual framework for identification, management, and the care of all patients with CKD, and those who are at risk for kidney failure. Operationally, CKD is defined as kidney damage or GFR < 60 ml/min/1.73m^2 for ≥ 3 months or more, regardless of underlying diagnosis. Kidney damage is usually identified by abnormalities in the blood, urine, and imaging tests and, if needed, by kidney biopsy. The most accessible early marker of CKD is an abnormal urinalysis, most specifically the presence of proteinuria. Persistent proteinuria is an important marker for kidney damage and has been identified as a risk factor for progressive losses in kidney function for both adults and children.[3–5]

Table 4.1 Criteria for the definition of chronic kidney disease (CKD)

A patient has CKD if either of the following criteria are present:

1. Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), indicated by one or more of the following:
   - Abnormalities by kidney biopsy
   - Abnormalities based on imaging tests
   - Abnormalities in the composition of the blood or urine
2. GFR < 60 ml/min/1.73 m^2 for ≥ 3 months, with or without the signs of kidney damage listed above

The NKF-K/DOQI Evaluation, Stratification and Classification Committee, utilizing an evidence-based review, and evaluation of data from the National Health and Nutrition Examination Survey (NHANES), devised a staging classification system for CKD. The goals of this staging system were to establish a common nomenclature for patients, general healthcare providers, and nephrologists in discussing CKD, anticipating comorbidities, and developing treatment plans for progressive kidney disease. The five different CKD stages correspond to the increasing severity of CKD (Table 4.2). Higher stages of CKD are associated with poorer kidney function and increasing likelihood of associated complications.

GFR in children varies with age, gender, and body size. GFR increases with maturation from infancy and approaches adult mean value by 2 years of age (Table 4.3).[6] Thus, it is important to recognize that GFR ranges that define the CKD stages apply only to children 2 years and above. These GFR ranges defining CKD do not apply to infants, since they normally have a lower GFR, even when corrected for body surface area.

Generally, the GFR can be approximated by estimating equations based on the age, height, and gender of the patient, as given by Schwartz formulas.[6] The GFR can also be estimated from a timed urine collection for creatinine clearance. However, the collection can be inconvenient for families and inaccurate due to missed samples and voiding problems. Thus, the accuracy of the GFR by a 24-hour urine collection is not necessarily improved over estimating equations. Estimation of the GFR by a timed urine collection is useful in the following clinical circumstances:

1. estimation of GFR in individuals with exceptional dietary intake (vegetarian diet, creatine supplements), or decreased muscle mass (amputation, malnutrition, muscle wasting)
2. assessment of diet and nutritional status
3. need to start dialysis.[6]

At each CKD stage, an action plan for strategies of evaluation and management has been recommended (see Table 4.2).

Table 4.3 Normal glomerular filtration rate (GFR) in children and adolescents

Age (sex)	Mean GFR ± SD (ml/min/1.73 m^2)
1 week (males and females)	41 ± 15
2–8 weeks (males and females)	66 ± 25
> 8 weeks (males and females)	96 ± 22
2–12 years (males and females)	133 ± 27
13–21 years (males)	140 ± 30
12–21 years (females)	126 ± 22

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Further discussion on clinical management of CKD is given in Chapter 22.

The NKF recommended that the word 'kidney' be used instead of 'renal' in the staging system, so as to facilitate communication in an easily understandable language. The public, patients, their families, and other healthcare professionals are able to easily understand the term 'kidney'. In contrast, the term 'renal' usually requires further clarification and explanation. Clearly, there is a need to bridge commonly used clinical terms such as chronic renal failure (CRF), chronic renal insufficiency (CRI), and end-stage renal disease with the CKD classification system.

Chronic renal failure or chronic renal insufficiency

Both of these terms denote a reduction in kidney function prior to needing dialysis. Although the threshold of GFR reduction where CRF or CRI begins is a matter of opinion, many registries have operationally defined this as a GFR below 75 ml/min/1.73 m^2. Hence, populations with CRI or CRF will be categorized between CKD stages 2–4.

Table 4.2 NKF-K/DOQI classification of chronic kidney disease

Stage	GFR (ml/min/1.73 m^2)	Description	Action plan[a]
1	≥ 90	Kidney damage with normal or increased GFR	Diagnose and treat primary and comorbid conditions, slow CKD progression, CVD risk reduction
2	60–89	Kidney damage with mild reduction of GFR	Evaluate rate of decline in GFR
3	30–59	Moderate reduction of GFR	Evaluate and treat complications
4	15–29	Severe reduction of GFR	Prepare for kidney replacement therapy
5	< 15 (or dialysis)	Kidney failure	Kidney replacement therapy

CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate.
[a]Includes actions from preceeding tables.
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End-stage renal disease

The term 'end-stage renal disease' refers to a severe, irreversible reduction in kidney function, usually requiring dialysis or kidney transplantation to sustain life. ESRD generally denotes a GFR <15 ml/min/1.73 m^2. Therefore, under the current classification scheme, CKD stage 5 parallels definition of ESRD. However, the term ESRD also has an operational and administrative meaning regarding treatment with dialysis or transplantation, particularly by the Medicare ESRD Program in the United States.

Epidemiology of kidney disease

Since CKD is usually asymptomatic in its early stages, it is both underdiagnosed and underreported. Consequently, it is difficult to estimate the incidence and prevalence of CKD. Large population-based studies in adults, such as the third NHANES, have allowed estimation of the prevalence of CKD in this population. These data have demonstrated that the burden of patients with ESRD in adults is growing at an alarming rate in the US population.[7] Figure 4.1 shows estimates of the number of Americans affected by various stages of CKD, according to NHANES data.[8,9] Given the available estimates, the prevalence of early stages of kidney disease (stages 1–4) is 10.8%, or approximately 100 times greater than the reported prevalence of ESRD or stage 5 CKD (0.1%).[10] A similarly higher prevalence of earlier stages of CKD (stages 1–4) compared with ESRD is believed to be present in the pediatric population also.

Data regarding the incidence and prevalence of CKD in the pediatric and adolescent population are few, but are beginning to emerge. Registries from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) and a population-based registry in Italy (ItalKid) are published sources that lend insight into the epidemiology of the early stages of CKD. In brief, the NAPRTCS is a collaborative research effort that began in 1987 and gathers data from pediatric nephrology centers in North America on pediatric transplants, CKD, and dialysis. ItalKid is a registry that has collected information from pediatric, pediatric nephrology, pediatric urology, pediatric surgery, and adult nephrology units throughout Italy since 1995. These data, taken together with existing ESRD databases, offer an insight into the epidemiology of CKD in children and adolescents.

Based on data from the ItalKid registry, the incidence of new cases of CRI is reported to be 12.1 (range 8.8–13.9) per year per million of the age-related population (MARP).[11] The estimate of prevalence of CRI in children and adolescents with CRI is 74.7 per MARP.[11] Both NAPRTCS and ItalKid data demonstrate a slower progression of early CKD towards ESRD in patients with congenital anomalies than in patients with glomerular disease. Further, the rapid progression is more commonly seen in patients with focal segmental glomerulosclerosis (FSGS).[11,12]

In the older published literature (pre 1990) it was reported that glomerular diseases and chronic pyelonephritis were the two leading etiologies of ERSD in children, each accounting for approximately 25% of cases.[13] However, more recent data from various registries demonstrate that structural urologic causes contribute the largest percentage of underlying disease, particularly in the youngest age groups.[14–17] The reported distributions of causes of CKD in childhood from various geographic areas are given in Table 4.4.

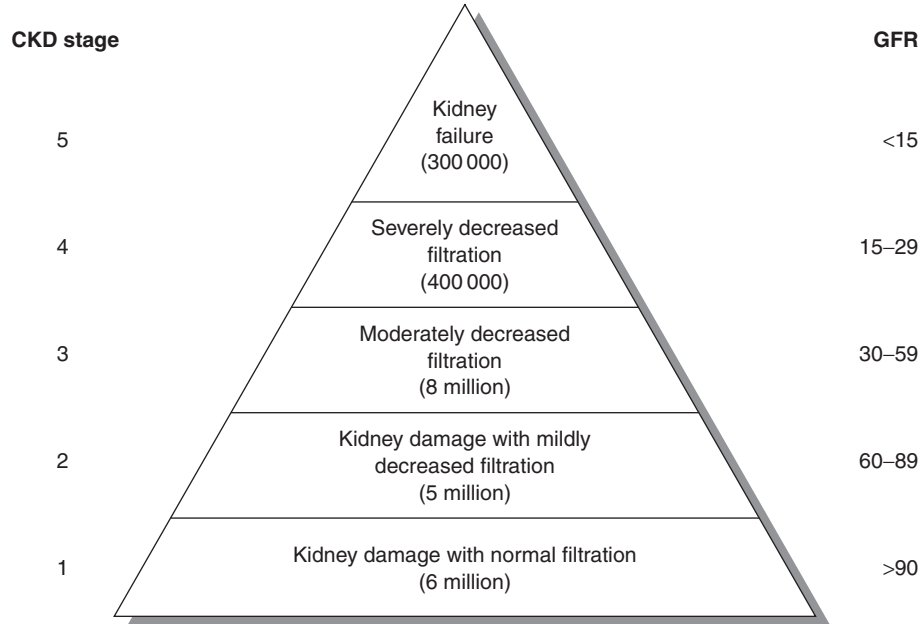

Figure 4.1 NKF/KDOQI stages of CKD: prevalence of chronic kidney disease (CKD) – US adult population estimates. GFR, glomerular filtration rate. (Reproduced from Coresh et al.[8] with permission from Elsevier.)

Table 4.4 Global perspective of chronic kidney disease (CKD): distribution of causes of CKD reported from non-North American countries

	Sweden	Venezuela	Mexico	South Africa
No. of patients	**118**	**255**	**211**	**109**
Glomerulopathies	14.5%	42%	49%	41%
Urinary tract anomalies:	23%	31%	19%	21%
Familial nephropathy	26%	16%	5%	16%
Multisystem disease	10%	4%	7%	9%
Renal hypo/dysplasia	18%	4%	5%	13%
Miscellaneous/unknown	8.5%	3%	15%	–

Data adapted from Esbjorner E, Berg U, Hansson S. Pediatr Nephrol 11:438, 1997,[14] Diniz JS. Pediatr Nephrol 2:271–6, 1988[28] and Grunberg J, Verocay C. Pediatric Nephrology: Williams and Wilkins; 1994:1432–4.[29]

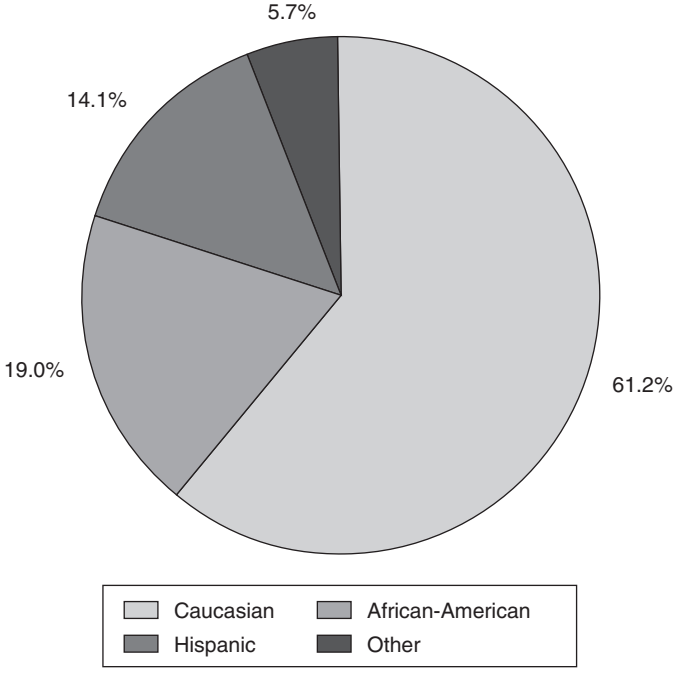

Figure 4.2 Prevalence of chronic kidney disease by race. Data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2004 Annual Data Report.[18]

NAPRTCS database

In the USA, the NAPRTCS 2004 Annual Report[18] described 5651 patients with CKD (excluding dialysis and transplant patients) in this database between 1994 and 2003, of which 64.4% are male. Racial breakdown is 61.2% Caucasian, 19.0% African-American, 14.1% Hispanic, and 5.7% other racial groups (Figure 4.2). Age distribution shows that 19.9% ($n=1124$) are infants (0–1 years), 16.4% ($n=925$) are toddlers (2–5 years), 32.6% ($n=1838$) are between 6 and 12 years old, and 31.0% ($n=1750$) are over the age of 12 years old. As delineated in Table 4.5, the most common causes are obstructive uropathy, renal dysplasia, reflux nephropathy, and FSGS.

The causes of CKD in children also vary according to age and race. For analytical purposes, we divided the patient population into four large primary disease categories (Table 4.6 and Figure 4.3): structural causes (59%), glomerulonephritis (8%), FSGS (8%), and 'Other' (25%). Glomerular diseases and FSGS are more common causes of CKD among adolescent black and Hispanic patients compared with adolescent white patients. Structural causes are most common in the <12 years old age group.

End-stage renal disease in children

According to the USRDS Annual Data Report 2004 (ADR),[7] during 2002, the incidence of pediatric ESRD was approximately 15 per million population. Among US children, African-Americans have higher rates of ESRD than Caucasians, particularly in the 15–19-year-old age group. Asian/Pacific Islanders and Native Americans have intermediate rates.

The above estimates exclude those children in the USA who develop kidney failure but do not initiate renal replacement therapy (RRT). They also do not reflect the substantial number of children who develop CKD in adolescence, but present with ESRD as young adults. For example, the 2004 USRDS ADR[7] shows that 13% of incident ESRD patients in 2002 are between the ages of 20 and 44 years old. Prior longitudinal studies of renal disease progression (Modification of Diet in Renal Disease (MDRD)[19] and African-American Study of Kidney Disease (AASK))[20] have suggested that the overall rate of decline in GFR in adult patients with CKD is approximately 3–5 ml/min/year. Therefore, many young adults presenting with ESRD are likely to have developed early stages of CKD in childhood or adolescence.

Recently reported data from pediatric renal registries in 12 European countries described 3184 patients under 20 years

Table 4.5 NAPRTCS: etiology of chronic kidney disease stages 2–4

Primary diagnosis	$n = 5651$[a]	Percent
Obstructive uropathy	1296	22.9
Aplasia/hypoplasia/dysplasia	1010	17.9
Reflux nephropathy	471	8.3
Focal segmental glomerulosclerosis (FSGS)	470	8.3
Polycystic kidney disease	234	4.1
Prune belly	173	3.1
Renal infarct	153	2.7
Hemolytic uremic syndrome	124	2.2
SLE nephritis	85	1.5
Cystinosis	85	1.5
Familial nephritis	82	1.5
Pyelo/interstitial nephritis	81	1.4
Chronic glomerulonephritis	71	1.3
Medullary cystic disease	67	1.2
Membranoproliferative glomerulonephritis – type 1	64	1.1
Berger's (IgA) nephritis	58	1.0
Congenital nephrotic syndrome	47	0.8
Idiopathic crescentic glomerulonephritis	42	0.7
Henoch–Schönlein nephritis	39	0.7
Membranoproliferative glomerulonephritis – type II	27	0.5
Membranous nephropathy	27	0.5
Other systemic immunologic disease	25	0.4
Wilms' tumor	22	0.4
Wegener's granulomatosis	15	0.3
Sickle cell nephropathy	12	0.2
Diabetic glomerulonephritis	10	0.2
Oxalosis	5	0.1
Drash syndrome	5	0.1
Other	709	12.5
Unknown	142	2.5

[a]All patients in the registry.
Reproduced with permission from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2004 Annual Data Report.[18]

Table 4.6 Etiology of chronic kidney disease stages 2–4 by primary diagnosis, and age in the United States

Race	Number of patients	Percent structural	Percent GN	Percent FSGS	Percent other
All patients	5641	59	8	8	25
0–1	1124	78	0	0	21
2–5	925	66	2	6	26
6–12	1838	61	6	7	25
> 12	1750	41	18	15	26
Missing	4	75	25	0	0

Data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2004 Annual Report.[18]
FSGS, focal segmental glomerulonephritis; GN, glomerulonephritis.

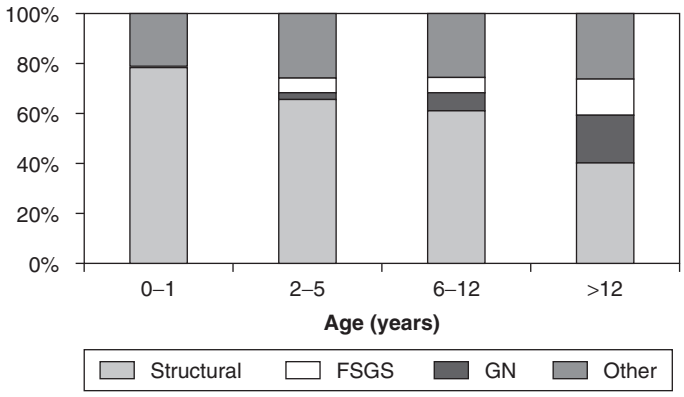

Figure 4.3 Etiology of chronic kidney disease (CKD) stages in NAPRTCS patients 2–4 by age. Data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2004 Annual Data Report.[18] FSGS, focal segmental glomerulonephritis; GN, glomerulonephritis.

of age who initiated RRT between 1980 and 2000. Overall, the incidence of RRT was 9–10 per MARP, being highest in the 15–19-year-old age group. The commonest causes were hypoplasia/dysplasia and hereditary disorders in the 0–4-year-old age group, with glomerulonephritis and pyelonephritis becoming increasingly common in the older age group of children.[21] Data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) similarly show congenital urologic disorders predominating among younger children, and reflux nephropathy and glomerular diseases being more common in the older adolescents.[22]

According to the USRDS 2004 ADR,[7] the mean age of initiation of dialysis in children was approximately 14 years for a patient with glomerulonephritis, and 9.4 years for a patient with congenital urologic disease. Diabetic nephropathy and hypertension are the most common causes of CKD in adults, but are very rare causes of CKD in childhood.

Global perspective of chronic kidney disease

According to a recent review,[23] about 90% of treated ESRD patients come from developed countries. Treated ESRD is much less frequent in less-developed countries that cannot allocate healthcare resources to RRT programs. The etiology of CKD in less-developed countries is also uniquely different. With an increased burden of infectious diseases in these regions, infection-related glomerulonephritis and consequent renal insufficiency is more common. In some parts of the world there are increasing numbers of individuals with CKD secondary to renal involvement from HIV, hepatitis C, malaria, schistosomiasis, and tuberculosis.

Recent reports from India on pediatric CRF patients[24] also describe obstructive and reflux nephropathy as the most common causes of CRF. Other reports from India[25] describe higher rates of glomerulonephritis, interstitial nephritis, and kidney disease secondary to hepatitis and tuberculosis than those reported from the USA and Western Europe. A 2003 report on CRF from Nigeria (1985–2000)[26] describes glomerulopathies and chronic glomerulonephritis as the major causes of CRF. Because of financial limitations, few of these patients were able to undergo kidney biopsy for pathologic diagnosis or have access to RRT, resulting in a higher mortality rate than that seen in developed countries.

Future needs

In order to slow progression of earlier stages of CKD to ESRD, and treat its complications during childhood and the productive young adulthood years of life, an in-depth understanding of the risk factors for progression of CKD in pediatrics is necessary. To this end, the NIH has funded adult and pediatric studies of CKD, the Chronic Renal Insufficiency Cohort (CRIC) study[27] in adults and the Chronic Kidney Disease in Children (CKiD) study. The CKiD study, a multicenter study of 540 children aged 1–16 years old with mild to moderately decreased kidney function, will focus on risk factors for CKD progression, identified during the key period spanning early decline in renal function (i.e. GFR 30–75 ml/min/1.73 m^2) to the development of ESRD. The study will obtain longitudinal data to determine the heterogeneity of rates of decline of renal function. The study will collect data on known risk factors for CKD progression, including causes of CKD, proteinuria, and hypertension, as well as collect biologic and genetic samples for future studies of cytokines or genetic polymorphisms that may yield scientific insight into the pathophysiologic mechanisms of CKD progression in both adults and children. In the CKiD study, concurrently collected data on neurocognitive function and cardiovascular risk factors will yield improved understanding of the sequence of associations between kidney disease progression, the development of cardiovascular comorbidity, and its impact on cognition, behavior, and quality of life for children.

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5 Clinical assessment of renal function

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Determination of renal function is necessary for diagnostic and prognostic evaluation of patients with kidney disease. Whereas precise determination of renal function is possible in experimental animals, investigations in humans need to be easy to use, reproducible, and clinically applicable. Urinalysis is considered to be the simplest test that can provide useful information regarding the basic functional status of the kidneys. Apart from urinalysis, this chapter also discusses the performance and interpretation of the most commonly used renal function tests in clinical use. Diagnostic imaging investigations also provide clinically relevant dynamic functional data. These investigations are discussed in detail in Chapters 6 and 7.

Urinalysis

In general, the most reproducible urine specimen is that obtained upon awakening from sleep, because it is not influenced as much by excessive fluid and protein intake. This is also essential when the clinician is concerned with urinary concentrating ability. It is often recommended for the parents to bring in the first morning urine from home when a child has difficulty urinating on command. Younger children should have a plastic bag attached to the perineum after admission to the office, to facilitate obtaining a sample in the absence of toilet training.

Commercially available dipsticks have simplified chemical analysis of urine. It needs to be mentioned that false-positive and false-negative tests can result with expired test strips, or if they have been stored inappropriately for a prolonged period. Urine samples should be grossly examined and tested for pH, specific gravity, protein, blood, glucose, and nitrites.

Appearance

Fresh urine generally ranges from pale yellow to deep amber. The color of urine may provide clues to several underlying renal and non-renal disorders (Table 5.1). Red discoloration may be caused by the presence of blood (hematuria), hemoglobin (hemoglobinuria), or myoglobin (myoglobinuria), but red blood cells (RBCs) are seen only in the urinary sediment of patients with hematuria. Urinary bleeding from the bladder or other parts of the collecting system tends to color the urine pink or red in color, whereas glomerular bleeding appears rusty brown (cola or tea colored). Red urine may also be seen in patients with porphyrias, as well as following intake of beets, certain food additives, or some drugs.

The urine is usually clear but it may be turbid due to the precipitation of phosphates in alkaline urine or uric acid in acid urine, especially upon chilling. Leukocytes can also render the urine cloudy.

Odor

The normal odor of urine is mildly aromatic. Bacterial infection may lead to a fetid or ammoniacal odor. Some disorders of metabolism cause particular odors in the urine, including aromas such as musty, sweet, sweaty-foot, fishy, and malt.

pH

Urine pH normally ranges from 4.5 to 8, depending on the acid–base and metabolic state. Freshly voided urine should be examined, since loss of carbon dioxide to air will falsely alkalinize the pH. Bacterial contamination may also change the baseline pH, depending on the metabolism of the particular organism. This dipstick determination of pH is adequate for assessing risk factors for kidney stones but is not usually accurate enough for assessing whether or not a patient has renal tubular acidosis (RTA). In this latter case, it is important to obtain blood pH (and/or bicarbonate) around the same time as the urine is collected, and the urine should be sent to the laboratory for pH determination by pH meter.

Specific gravity and osmolality

Urine osmolality is the key indicator of urinary concentration, and is maximal after an overnight thirst (> 870 mOsm/kg in children > 2 years).[1] Urine osmolality is determined from the concentration of solutes in the urine, which includes primarily salts and urea. Determination of the osmolality on thirsting samples frequently can eliminate the possibility of a defect in urinary concentration and should be performed before embarking

Table 5.1 Conditions associated with abnormal coloration of the urine

Pathology	Ingestion of drugs or food
Red–Burgundy–Pink	
Gross hematuria	Anthocyanin pigment
Papillary necrosis (often with clots)	Rhodamine B
	Blackberries
Hemoglobinuria, hemolysis	Beets
Myoglobinuria	Phenophthalein
Porphyria	Pyridium
Menstrual contamination	Aminopyrine
Serratia marcescens	Phenytoin sodium
Urates	Azo dyes
Dark Brown or Black	
Homogentisic aciduria	Aniline
Alkaptonuria	Cascara
Methemoglobinemia	Resorcinol
Melanin	Senna
Tyrosinosis	Thymol
Phenol poisoning	Hydroxyquinone
Blue–Green	
Obstructive jaundice	Methylene blue
Blue diaper syndrome	Indigo-carmine
Hepatitis	Resorcinol
Pseudomonas infections	Tetrahydronaphthalene
Phenol poisoning	Methocarbamol
Indicans (indoxyl sulfate)	Carotene
	Riboflavin
	Chlorophyll
	Concentrated yeast
Cloudy–Milky	
Nephrotic syndrome	
Chyluria	
Pyuria	
Bacteria, yeasts	
Urates, uric acid (acid pH)	
Calculi, 'gravel' (phosphates, oxalates)	
Clumps of pus, tissue	
Fecal contamination	
Radiographic dye (acid pH)	
Elephantiasis	

Data from Goldsmith DI. Clinical and laboratory evaluation of renal function. In: Edelmann CM Jr, ed. The Kidney and the Urinary Tract. Boston: Little Brown and Company; 1978: 213; and Kher KK. Urinalysis. In: Kher KK, Makker SP, eds. Clinical Pediatric Nephrology. New York: McGraw-Hill; 1992: 23.

on more extensive testing. Osmolality may be decreased in renal insufficiency, as well as in states of central and nephrogenic diabetes insipidus. However, osmolality is not routinely measured. In most situations osmolality can be approximated from specific gravity according to the formula:[1]

$$\text{Osmolality} = (\text{specific gravity} - 1.000) \times 40\,000$$

However, protein, glucose, and osmotic contrast agents contribute more to the weight of the urine than to the osmolality, and therefore alter the above relationship. In these cases, osmolality is the preferred measurement to assess urinary concentrating ability.

Protein

Normally, the glomerulus restricts the filtration of proteins based on size and charge (Figure 5.1A). Size selectivity of the glomerular capillary is largely determined by the endothelial glycocalyx and the epithelial slit draphragms (Figure 5.1B), and passibly by the glomerular basement membrane.[2] The permeability to proteins also depends on electrical charge; the glomerular capillary wall is charged negatively due to its rich heparan sulfate content.[3,4] Negatively charged macromolecules are more restricted than neutral or positively charged molecules of similar molecular weight.[2,4] The electrical charge has less influence on smaller molecules such as ions. It is well known that the massive proteinuria of nephrotic syndrome is due to impaired barrier charge and size selectivity.[3,4] Most proteins that are filtered are reabsorbed by endocytosis of the proximal tubule. But this process can saturate when the amount of filtered proteins is large.

Tamm–Horsfall protein (uromodulin) is a constituent of urinary protein in normal individuals.[5] This glycoprotein is secreted by the thick ascending limb of the loop of Henle and forms the matrix of urinary casts. Proteinuria is an important indicator of renal disease in children and, in patients with disorders other than minimal change nephrotic syndrome, it correlates well with the severity of renal disease.[6–8] Proteinuria may be classified as being glomerular, tubular, or overflow proteinuria.

Glomerular proteinuria

Damage to the permselective glomerular barrier results in the passage of an increased fraction of plasma proteins through the glomerular pores. The filtered protein exceeds the reabsorptive capacity of the proximal tubule and results in proteinuria. Glomerular proteinuria may be selective, and is composed chiefly of albumin (MW = 67 000 Da). In contrast, non-selective glomerular proteinuria is composed of proteins exceeding 67 000 Da, such as transferrin, and immunoglobulin G. In general, urine from steroid-sensitive minimal change nephrotic syndrome is highly selective, whereas selectivity is low in orthostatic proteinuria[9–11] and focal segmental glomerulosclerosis.[12] However, the clinical utility of selectivity of proteinuria determined by IgG/albumin or transferrin/albumin ratios is not clearly established (also see Chapter 9).

Tubular proteinuria

Impaired proximal tubular reabsorption of low-molecular-weight proteins (MW < 40 000 Da) results in tubular proteinuria. This is observed in the renal Fanconi syndrome as well as in drug (aminoglycosides) or heavy metal intoxication. Markers of tubular proteinuria include β_2-microglobulin (MW = 11 800 Da), α_1-microglobulin (MW = 30 000 Da),

lysozyme (MW = 14 400 Da), and retinol-binding protein (MW = 21 400 Da).

Overflow proteinuria

Overflow proteinuria may be seen with an unusual increase in protein filtered load, such as with hemoglobinuria, myoglobinuria, or Bence Jones proteinuria (multiple myeloma).

Quantitation of proteinuria

Dipstick detection of proteinuria is accomplished using indicator strips impregnated with tetrabromophenol blue. When urinary protein binds with the dye in the test strip, there is a color change from yellow to green. This test correlates well with the degree of albuminuria, and may not detect other urinary proteins to the same degree as albumin. False-positive results occur in alkaline urine, or when urine is contaminated with quarternary ammonium salts such as chlorhexidine. Proteinuria can also be detected by using 10% sulfosalicylic acid, which precipitates urinary protein (Table 5.2). This semiquantitative assessment of the urine's turbidity correlates well with total urinary protein, including albumin. This method is particularly useful for detecting tubular, and overflow proteinuria in the office.

Proteinuria is usually quantified by autoanalyzer-adapted turbidimetry, using benzethonium chloride to precipitate the urinary proteins at an alkaline pH. Albumin is quantified by various immunochemical assays, although high-performance liquid chromatography (HPLC) analysis is better able to detect albumin-derived peptides that are immunounreactive, allowing for earlier diagnosis of microalbuminuria.[13] Urine protein electrophoresis can also be used to distinguish glomerular, tubular, and overflow proteinuria.

Urine protein excretion can be quantified by obtaining the protein/creatinine ratio, measured in a random or first morning sample. The urinary protein/creatinine (mg/mg or unitless) ratio correlates well with the 24-hour urine protein excretion.[7,9,14–17] The normal value for the urinary protein/creatinine is <0.2, but is slightly higher in younger children (Table 5.3). Proteinuria is considered of nephrotic range if the protein/creatinine ratio exceeds 2.0.[15,16] The normal value for 24-hour urine protein excretion is <100mg/m^2/day, and nephrotic range proteinuria exceeds 1000mg/m^2/day.[18] Urinary microalbuminuria, used to screen children with diabetes of ≥5 years' duration, is expressed as an albumin/creatinine ratio, and is normally <30mg/g of creatinine.[6,19]

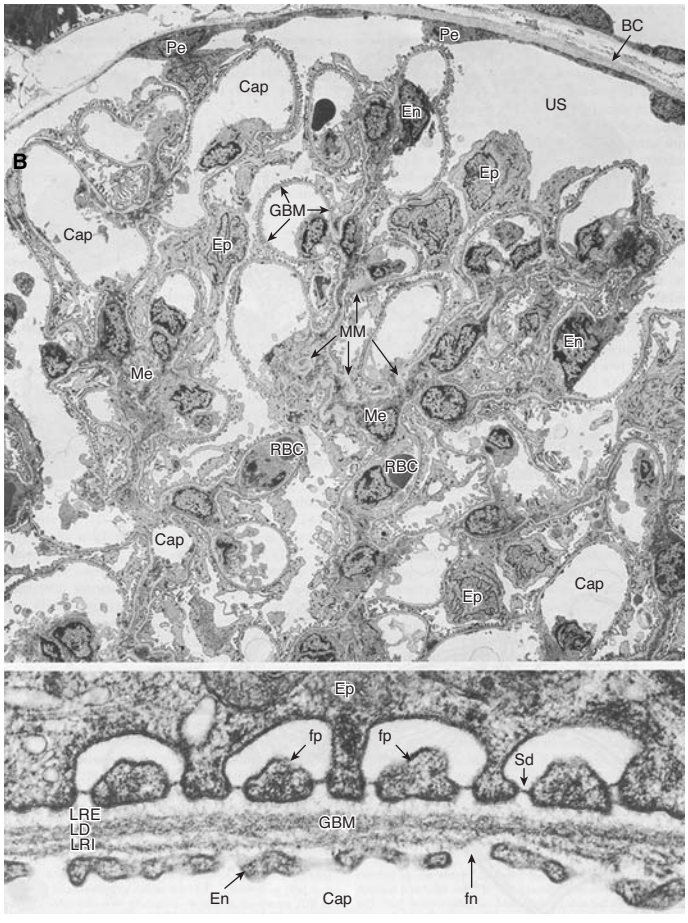

Figure 5.1 The glomerulus. (A) Low-power electron micrograph of glomerular capillaries (Cap). Capillaries are made of three cell types – visceral epithelial (Ep), endothelial (En), and mesangial (Me) cells – and two extraglomerular matrices – glomerular basement membrane (GBM) and mesangial matrix (MM). Parietal epithelium (Pe) lines Bowman capsule (BC) from inside. RBC, red blood cell. (B) High-magnification electron micrograph of the ultrafiltration unit, consisting of epithelial foot processes (fp) of epithelial cells (Ep) with intervening slit diaphragms (Sd), GBM, and fenestrated (fn) endothelium (En). GBM consists of lamina densa (LD), lamina rara interna (LRI), and lamina rara externa (LRE). (Reprinted with permission from Macmillan Publishers Ltd: Lab Invest. Biophysiology of glomerular filtration and proteinuria. 1984.[4])

Blood

Dipsticks have been used to detect the presence of hemoglobin in the urine. The reaction relies on the peroxidase-like activity

Table 5.2 Semiquantitative determination of urinary protein using the sulfosalicylic acid precipitation test

Degree of turbidity	Reading	Estimated proteinura (mg/dl)
No turbidity	Negative	No proteinuria
Slight turbidity	Trace	1–20
Turbid (newsprint visible)	1+	30
White cloud (heavy lines visible)	2+	100
Fine precipitate (heavy lines invisible)	3+	300
Flocculent precipitate (like yogurt)	4+	>500

This test is conducted by adding 10 drops of 10% sulfosalicylic acid to 10 ml of urine. Sulfosalicylic acid detects all urinary proteins, including albumin.

Table 5.3 Urinary protein/creatinine ratio in normal children, showing 95th percentile values of the ratio in various age groups

Age (years)	Protein (mg/mg creatinine)
<2	0.492
2–13	0.178
>13	0.178

Table adapted from Houser.[16]

of hemoglobin to catalyze the reaction of a hydroperoxide with tetramethylbenzidine to give a green-blue color; myoglobin will also give a positive reaction. The sensitivity is such that a negative test rules out significant hematuria. A positive test indicates the presence of intact RBCs, hemoglobin, or myoglobin, and the identification of RBCs requires further examination by microscopic analysis. If no RBCs or ghosts are identified, and contamination has been ruled out, the differentiation between hemoglobinuria and myoglobinuria can be accomplished using immunochemical methods.

Glucose

Urine glucose is generally measured using dipsticks based on the oxidation of glucose by glucose oxidase. False-negative results occur if there are large quantities of reducing agents such as vitamin C, tetracyclines, or homogentisic acid in the urine. False-positive results have not been reported.

Nitrite

More than 90% of common urinary pathogens are nitrite-forming bacteria. Nitrite can be detected in urine using a dipstick containing *p*-arsanilic acid, which reacts with nitrite to generate a diazonium compound that is then converted to 3-hydroxy-1,2,3,4-tetrahydrobenzo-quinoline-3-ol to produce a pink azo dye. A false-positive reading will occur if bacterial overgrowth is allowed to develop during delayed transit before testing. False-negative results occur in the presence of ascorbic acid or if frequent voiding of dilute urine does not allow sufficient time for nitrite to be produced.

Microscopic analysis of urine

The microscopic examination of the urine is no longer quantified as the rate of excretion of formed elements (Addis counts), but is used semiquantitatively to confirm the detection of hemoglobin by dipstick and identify the presence of cellular casts, crystals, and bacteria.

Technique

A 10 ml sample of fresh urine is centrifuged at 1100–1300 *g* for 5 min, the supernatant decanted, and the pellet resuspended in the remaining 0.25 ml of urine. An aliquot is pipetted onto a slide and coverslipped. Examination first using a low-power objective (10×) permits a gross assessment of cells, casts, and crystals, and this should include a systematic view along the edges of the coverslip, where casts tend to accumulate. The number of casts is generally expressed per low-power field (lpf). Switching to a high-power objective (40×) permits determination of the cellular constituents of the casts and the specific forms of crystals. Then, an examination of 5 random fields at 40× throughout the slide permits one to assess the number of cells per high-power field (hpf). Counting chambers are rarely used now in offices or clinical laboratories. Microscopic analysis of urine that is more than 1 hour old is unlikely to provide reliable quantitative information.

Red blood cells

In healthy children, the normal upper limit for the number of RBCs in fresh midstream urine is <2 RBCs/hpf. The morphology of the cells is helpful to distinguish between glomerular and non-glomerular hematuria. Dysmorphic RBCs with large variation in size and shape and hemoglobin content are more likely to be seen with glomerulonephritis (Figure 5.2A). Eumorphic red blood cells (normal-appearing) are more likely to be observed in non-glomerular urinary bleeding due to stones, hypercalciuria, and trauma[20] (Figure 5.2B). Whereas phase contrast microscopy is best utilized for this analysis, a standard lens can be used, provided that the light (and possibly the condenser) can be racked down to provide better contrast (Figure 5.2C, arrowhead).

White blood cells

In healthy children, the upper limit of normal for the number of white blood cells (WBCs) in a fresh midstream urine is 2 WBCs/hpf. Neutrophils are the predominant WBC in the urinary sediment, except in cases of allergic interstitial nephritis, which is often associated with increased numbers of eosinophils in the urine. Lymphocytes may be present in urine during acute transplant rejection. WBCs can be identified by standard microscopy using a 40× objective by the presence of a nucleus and a granular appearance to the cytoplasm (Figure 5.2C, short arrow).

Renal epithelial cells

Epithelial cells from the renal tubules, collecting system, or the bladder can be identified by their large size, polygonal shape, and single round nucleus. Whereas renal tubular epithelial cells are only slightly larger than WBCs, bladder epithelial cells are three to four times the size of leukocytes and may appear folded upon themselves along edges. In nephrotic syndromes, renal tubular epithelial cells may appear granular due to the accumulation of proteins or lipids in cytoplasmic vesicles. Increased renal epithelial cells may be seen in the setting of renal tubular injury (acute tubular necrosis) or any forms of renal parenchymal disease (acute pyelonephritis).

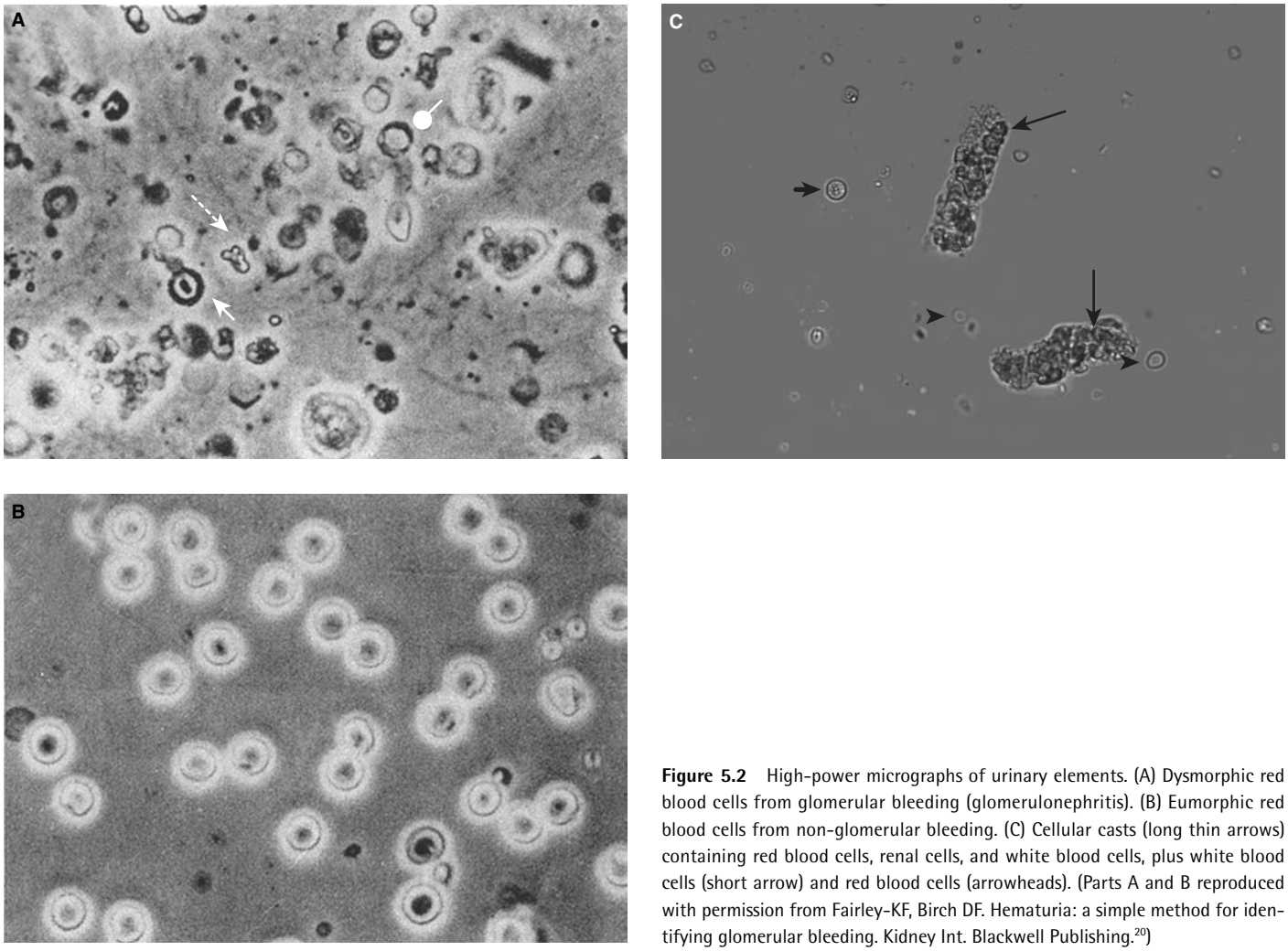

Figure 5.2 High-power micrographs of urinary elements. (A) Dysmorphic red blood cells from glomerular bleeding (glomerulonephritis). (B) Eumorphic red blood cells from non-glomerular bleeding. (C) Cellular casts (long thin arrows) containing red blood cells, renal cells, and white blood cells, plus white blood cells (short arrow) and red blood cells (arrowheads). (Parts A and B reproduced with permission from Fairley-KF, Birch DF. Hematuria: a simple method for identifying glomerular bleeding. Kidney Int. Blackwell Publishing.[20])

Casts

Casts are cylindrical structures with a visible matrix that are formed in the renal tubules by the precipitation of Tamm–Horsfall protein. Cells may be trapped within the matrix, giving rise to cellular casts (see Figure 5.2C). Granular casts result from degeneration of cells within the casts. Cellular casts are classified according to the principal cell included therein (RBC, WBC, or epithelial cell). Hyaline casts are derived from Tamm–Horsfall protein and appear as translucent cylindrical structures. These may be seen in concentrated urine of normal children, as well as in fever, exercise, dehydration, diuretic use, congestive heart failure, and nephrotic syndrome.

WBC casts are commonly observed in acute pyelonephritis, tubulointerstitial diseases, glomerulonephritis (e.g. postinfectious glomerulonephritis) and acute renal transplant rejection. RBC casts appear as round discoid red cells embedded in the Tamm–Horsfall matrix. RBC casts are identified by the hemoglobin pigment within the matrix of the cylindrical cast and are pathognomonic of glomerular hematuria. Frequently, granular pigmented casts (brownish), composed of degenerating RBCs with varying hemoglobin content, may be observed in glomerulonephritis.

Waxy casts are similar to hyaline casts but are broader in size. They are commonly seen in chronic renal diseases. Large waxy casts (broad casts) are often seen in chronic renal failure. Broad casts are believed to originate in damaged nephron segments, or from the collecting system. Fatty casts result from the incorporation of fat within the Tamm–Horsfall matrix. Cholesterol droplets within these casts appear as Maltese cross structures when viewed under polarized light. Fatty casts are common in nephrotic syndrome. The urine of such patients may also contain oval fat bodies, structures which are fat-laden denuded renal tubular epithelial cells.

Bacteriuria

Significant bacteriuria can usually be detected using a 40× objective. Budding yeast forms (*Candida albicans*) can also be viewed at this power.

Crystals

Hypercalciuria[21] and hyperuricosuria[22] have both been implicated in the etiology of hematuria, and the urinary sediment in these clinical conditions may demonstrate calcium oxalate and uric acid crystals. An occasional calcium oxalate crystal can be observed in normal urine, although they are more prominent in hyperoxaluria, and some forms of hypercalciuria, especially in an acid urine (Figure 5.3A and 5.3B). Most kidney stones are composed of calcium oxalate, but a small percentages of stones

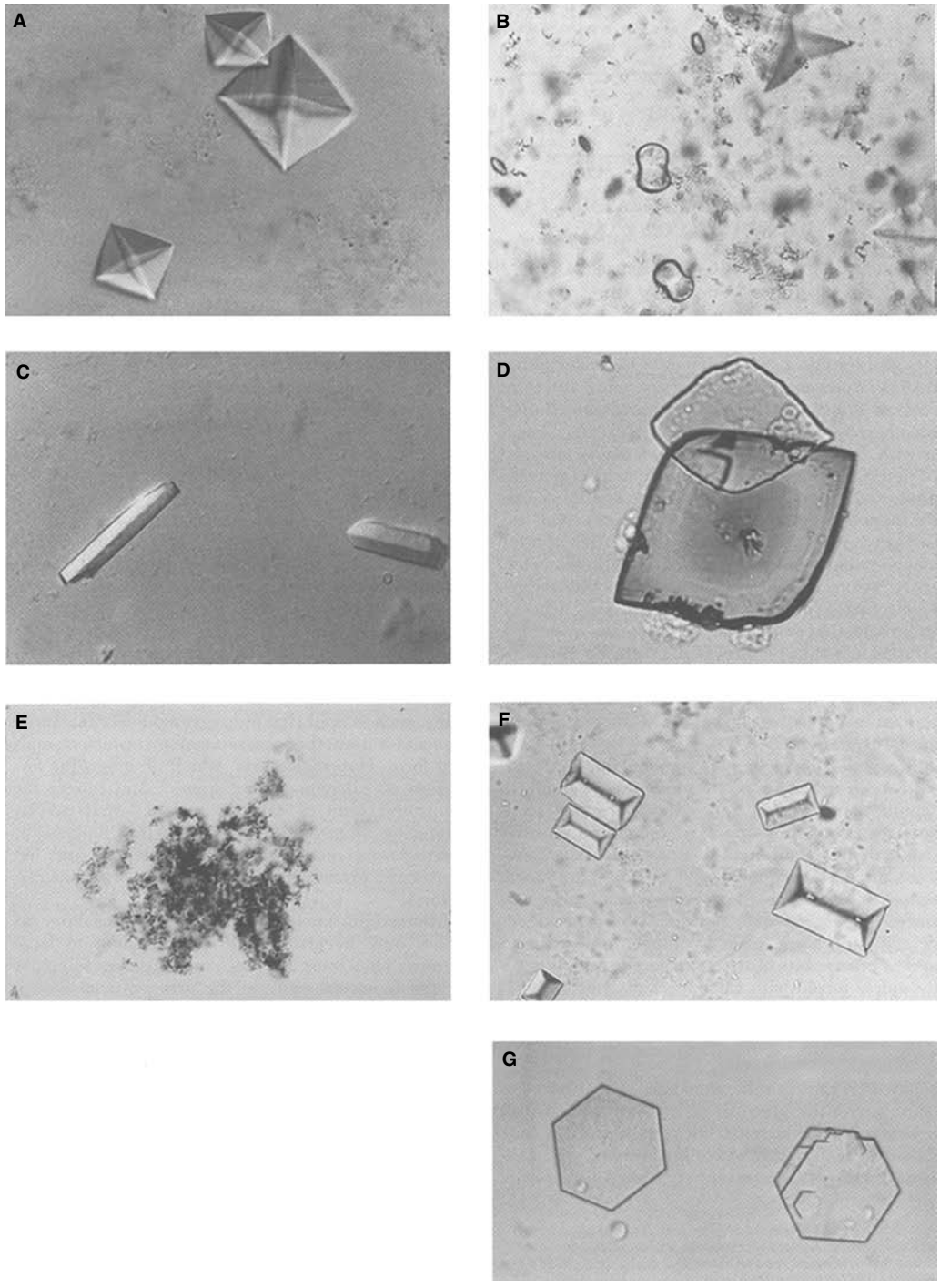

Figure 5.3 Urinary crystals commonly observed in patients with kidney stones. (A) Calcium oxalate dehydrate. (B) Calcium oxalate monohydrate dumb-bell-shaped crystals. (C) Elongated lath-shaped brushite crystals. (D) Rhomboidal uric acid crystals. (E) Uric acid microcrystals. (F) Coffin-lid-shaped struvite crystals. (G) Hexagonal cystine crystals. (Reproduced with permission from Coe et al.[23] Copyright © 1992 Massachusetts Medical Association.)

contain some uric acid and struvite (magnesium ammonium phosphate) seen in urinary tract infections with bacteria that produce the enzyme urease.[23] Some urinary stones contain calcium monohydrogen phosphate (brushite) crystals, which are seen as elongated thin strips (Figure 5.3C). The amorphous plates, diamonds, and trapezoids of uric acid crystals often appear orange and can be identified in acid urine by experienced microscopists (Figure 5.3D and 5.3E). Struvite crystals are seen in alkaline urine as 'coffin lids' (Figure 5.3F). The hexagonal crystals of cystinuria in acid urine (Figure 5.3G) (cystine stone formers) and fine needle-like crystals in tyrosinosis (tyrosinemia) are useful in making a diagnosis. The amorphous crystals of calcium carbonate, seen in hypercalciuria in an alkaline urine, can be easily solubilized in acid.

Glomerular filtration rate

Determination of glomerular filtration rate (GFR) is the most commonly employed and best clinical test for estimation of functioning renal mass. Knowledge of GFR enables the clinician to determine the progression of renal disease, predict the development of end-stage renal disease (ESRD), adjust medications excreted by the kidney, and to rationally prescribe fluids and solutes.

Physiology of glomerular filtration

Approximately 20% of the cardiac output flows through the two million glomerular capillary units of the two kidneys.[3] The glomerulus consists of a tuft of capillaries interposed between the afferent and efferent arterioles. The glomerular capillary wall through which the filtrate must pass is made up of three layers: the fenestrated endothelial cell, the glomerular basement membrane (GBM), and the epithelial cell (see Figure 5.1A). The epithelial cells are attached to the GBM by discrete foot processes, or podocytes. The pores between the foot processes, or slit pores, are covered by a thin membrane called the slit diaphragm (Figure 5.1B).[3,4,24] The GBM is derived from material produced by endothelial and epithelial cells, including type IV collagen, laminin, nidogen, and heparan sulfate proteoglycans. Laminin and nidogen form a tight complex to promote cell adhesion. The anionic heparan sulfate proteoglycans serve as the electrical charge barrier to the filtration of anionic macromolecules.[3,4]

One of the primary functions of the glomerulus is to allow the filtration of small solutes such as sodium and urea and water while restricting the passage of larger molecules. This permits the kidney to maintain homeostasis by excreting the nitrogenous waste derived from dietary intake, while preserving the essential larger plasma protein molecules. Solutes up to the size of inulin (MW = 5200 Da) are freely filtered, whereas myoglobin (MW = 17 000 Da) is filtered less completely than inulin, while albumin (MW = 67000 Da) is filtered only to a minor degree. Filtration is also limited for ions or drugs that are bound to albumin.

Starling forces

GFR is determined by two factors: the filtration rate in each nephron, also referred to as single-nephron GFR (SNGFR), and the number of filtering nephrons. Each normal kidney in humans is endowed with approximately one million units at birth. Blood entering through the afferent arteriole goes through the glomerular capillary tuft and exits through the efferent arteriole. Along the glomerular capillary tuft a portion of the glomerular filtrate is ultrafiltered into Bowman space, which after being processed by renal tubules and collecting duct, leads to the formation of urine. Fluid movement across the glomerulus is governed by Starling's forces, being proportional to the permeability of the glomerular capillary wall and to the balance between hydraulic and oncotic pressure gradients:

$$\begin{aligned}\text{SNGFR} &= L_pS\,(\Delta\text{hydraulic pressure} - \Delta\text{oncotic pressure})\\ &= L_pS\,[(P_{gc} - P_{bs}) - s(\pi_p - \pi_{bs})]\end{aligned}$$

where L_p is the unit permeability (or porosity) of the capillary wall; S is the surface area available for filtration; P_{gc} and P_{bs} are the hydraulic pressures in the glomerular capillary and in Bowman space, respectively; π_p and π_{bs} are the oncotic pressures in the plasma entering the glomerulus and in Bowman space, respectively; and s is the reflection coefficient of proteins across the capillary wall, ranging from 0 (completely permeable) to 1 (or completely impermeable). With the filtrate being essentially protein-free, $\pi_{bs} = 0$ and s is 1, so that:

$$\text{SNGFR} = L_pS\,(P_{gc} - P_{bs} - \pi_p)$$

The L_pS in the glomerular capillary is 50–100 times that of a muscle capillary and the capillary hydraulic pressure and mean gradient favoring filtration ($P_{gc} - P_{bs} - \pi_p$) is much greater in the glomerulus than in a muscle capillary.[24,25] These factors contribute to the high rate of filtration across the glomerular capillaries.

The plasma oncotic pressure (π_p) rises in response to the ultrafiltration of protein-free fluid. After the filtration of 20% of the nephron plasma flow, filtration equilibrium is normally achieved. Further filtration at this point ceases because the plasma oncotic pressure equals the hydraulic pressure within the glomerular capillaries, and there is no net ultrafiltration pressure. Thus, the presence of filtration equilibrium means that renal plasma flow is a major determinant of GFR.[3,24,25]

Size selectivity

The glomerular barrier filters molecules based on their size and charge. The GBM, endothelial glycocalyx and the slit diaphragms contribute to size selectivity.[2,3,4,26] The size limitation in the GBM represents functional pores in the spaces between the tightly packed cords of type IV collagen.[4] Cellular elements and slit diaphragms also play an important role in limiting the passage of macromolecules.[3,4,26] Most pores of the glomerular capillary wall are relatively small (mean radius = ~4.2 nm). They

partially restrict the filtration of albumin (mean radius = 3.6 nm) but allow the passage of smaller solutes and water. The endothelial cells do not contribute to size selectivity because the endothelial fenestrae are relatively wide open and do not restrict the passage of macromolecules with a radius under ~40 nm.[27] However, endothelial cells contribute significantly to charge selectivity (see below). Modeling of the glomerular filtration barrier suggests that the major portion of the capillary wall functions as an isoporous membrane, but that a very small fraction of the filtrate passes through larger pores.[2]

Charge selectivity

Molecular charge is the second major determinant of filtration across the GBM.[3,4,26] The inhibitory effect of charge is due to the electrostatic repulsion by anionic heparan sulfate proteoglycans both in the endothelial fenestrae and GBM (produced by both glomerular epithelial and endothelial cells).[3,4,28] Filtration of albumin is restricted to about 5% of that of neutral dextran of a similar molecular radius, suggesting that molecular charge is important in limiting the glomerular filtration of albumin.

Assessment of glomerular filtration rate

Since the total kidney GFR equals the sum of the SNGFRs in each of the functioning nephrons, the total GFR can be used as an index of functioning renal mass. Following nephron loss, compensatory changes in surviving nephrons are commonly observed in clinical practice. This leads to lesser loss of total renal function than anticipated by the extent of anatomic damage. For example, a loss of half the functioning nephrons leads to a decrease in GFR of only 20–30%, rather than the anticipated 50%. In most patients with early chronic kidney disease (CKD), the fluid and electrolyte balance is well maintained and even the urinalysis may be normal at times. The decline in GFR may, therefore, be the earliest and only clinical sign of renal disease. Serial monitoring of GFR can be used to estimate severity and monitor the course of CKD. Measurement of GFR is also useful in determining the appropriate dosage of drugs that are excreted by the kidney.

Concept of clearance

GFR represents the volume of plasma ultrafiltrate presented to the nephrons per unit time, in the process of urine formation. The most common measurement of GFR is based on the concept of clearance, which is defined as the equivalent volume of plasma from which a substance would have to be totally removed to account for its rate of excretion in urine per unit of time. The renal clearance of a substance x (C_x) is calculated as:

$$C_x = U_x V / P_x$$

where V is the urine flow rate (ml/min) and U_x and P_x are the urine and plasma concentrations of substance x, respectively. C_x is expressed as ml/min, and is usually normalized to a standard 1.73 m^2 idealized adult body surface area (i.e. C_x is in ml/min/1.73 m^2) by the factor 1.73/BSA, where BSA is the body surface area (in m^2) of the examined subject.

In order for the plasma clearance to be equal to the GFR, a marker must be freely permeant across the glomerular capillary, uncharged (neutral electrical charge), biologically inert (i.e. neither synthesized nor degraded by the kidney), and neither secreted nor reabsorbed by the renal tubule. The renal excretory rate of such an ideal marker x equals the rate of x filtered across the glomerulus:

$$P_x GFR = U_x V$$

or

$$GFR = U_x V / P_x$$

which is the clearance rate of substance x.

Inulin clearance

The fructose polysaccharide inulin, which has a mean molecular radius of 1.5 nm and a MW of approximately 5200 Da, is considered an ideal marker and the gold standard for measuring GFR. Inulin is freely filtered, is not protein-bound, is not reabsorbed, and is neither secreted nor metabolized by the kidney. When injected intravenously, inulin clearance equals GFR ($C_x = C_{In} = GFR$).[29]

The classic (standard) inulin clearance requires an intravenous priming dose of inulin, followed by a constant infusion to establish a steady-state inulin plasma concentration.[30] After an equilibration for ~45 minutes, serial urine samples are collected every 10–20 minutes through an indwelling bladder catheter. Insertion of an indwelling urinary catheter may not be possible or justifiable in current clinical practice, and urine is obtained voluntarily in such cases every 20–30 minutes, as dictated by the urge of the patient to urinate. High urine flow is maintained throughout the test by providing an initial oral water load of 500–800 ml/m^2, and replacing urinary water loss with oral intake of water (ml/ml).[31] Table 5.4A shows values of GFR in normal infants and children: see also Table 5.4B, which is described later.

In children with potential kidney disease, the use of inulin clearances has some limitations. First, some children may not be toilet trained and are unable to provide accurate collections of timed urine. Secondly, urologic problems are common causes of CKD in infants and young children,[32] and many of these children have significant vesicoureteral reflux, neurogenic bladders, and bladder dyssynergia. Collecting timed urine in such patients is difficult and fraught with error. Thirdly, technical difficulties encountered in performing inulin infusions and in reaching a steady state of inulin distribution are common.

Table 5.4A Glomerular filtration rate in normal infants and children, assessed by inulin clearance

Age	Mean GFR ± SD (ml/min/1.73 m^2)
Pre-term babies:	
1–3 days	14.0 ± 5[a]
1–7 days	18.7 ± 5.5[b]
4–8 days	44.3 ± 9.3[c]
3–13 days	47.8 ± 10.7[d]
8–14 days	35.4 ± 13.4[b]
1.5–4 months	67.4 ± 16.6[d]
Term babies:	
1–3 days	20.8 ± 5.0[b]
3–4 days	39.0 ± 15.1[e]
4–14 days	36.8 ± 7.2[f]
6–14 days	54.6 ± 7.6[g]
15–19 days	46.9 ± 12.5[b]
1–3 months	85.3 ± 35.1[e]
0–3 months	60.4 ± 17.4[h]
4–6 months	87.4 ± 22.3[h]
7–12 months	96.2 ± 12.2[h]
1–2 years	105.2 ± 17.3[h]
Children:	
3–4 years	111.2 ± 18.5[h]
5–6 years	114.1 ± 18.6[h]
7–8 years	111.3 ± 18.3[h]
9–10 years	110.0 ± 21.6[h]
11–12 years	116.4 ± 18.9[h]
13–15 years	117.2 ± 16.1[h]
2.7–11.6 years	127.1 ± 13.5[c]
9–12 years	116.6 ± 18.1[e]
Young adults:	
16.2–34 years	112 ± 13[i]

Data compiled from the following references:
[a]Brion LP et al. J Pediatr 109:698, 1986
[b]Guignard JP et al. J Pediatr 87:268, 1975
[c]Barnett HL et al. Pediatrics 3:418, 1949
[d]Barnett HL et al. Proc Soc Exp Biol Med 69:55, 1948
[e]Richmond JB et al. Proc Soc Exp Biol Med 77:83, 1951
[f]Broberger U. Acta Paediat Scand 62:625, 1973
[g]McCrory WW et al. J Clin Invest 31:257, 1952
[h]Brodehl J et al. Clin Nephrol 17:163, 1982
[i]Gibb DM et al. Clin Chim Acta 182:131, 1989.

Furthermore, inulin assay is not very specific and is potentially hazardous (boiling acid reagents), and there may be errors in accurately measuring inulin concentrations in plasma. These problems have rendered the standard inulin clearance to be impractical in children.

Constant infusion technique without urine collection

The clearance of a substance relates to its removal from the blood. Therefore, it is possible to determine the plasma clearance when the marker substance is infused at a constant rate, and a steady state is achieved. The constant infusion technique has utilized inulin, but other markers can also be used (see below). After equilibration of the marker in its distribution space, the excretion rate equals the infusion rate, and clearance can then be calculated from the rate of infusion and the concentration in plasma:[33]

$$C_x = I_x R / S_x$$

where I_x is the infusion concentration of the marker x, R is the infusion rate (ml/min), S_x is the serum concentration of x, and C_x is the clearance in ml/min/1.73 m^2. The constant infusion method overestimates GFR if steady-state concentration of the marker is not achieved.

Table 5.4B Plasma ^{51}Cr-EDTA clearance in normal children

Age (years)	Mean GFR ± SD (ml/min/1.73 m^2)
< 0.1	54.6 ± 14.1
0.1–0.30	65.2 ± 14.4
0.31–0.66	81.8 ± 19.2
0.67–1.00	103.8 ± 20.1
1.00–1.50	116.6 ± 28.3
1.51-2.00	111.5 ± 19.8
>2.00	113.9 ± 24.4

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Endogenous creatinine clearance and the use of cimetidine

Because of the difficulties with administering and measuring inulin, standard endogenous creatinine clearances have been used to estimate GFR. Endogenous creatinine clearance provides an acceptable measurement of GFR for clinical purposes and is calculated by the following equation:

$$C_{Cr} = U_{Cr} V / S_{Cr}$$

where C_{Cr} is creatinine clearance, U_{Cr} is urinary creatinine concentration, V is flow rate of urine in ml/min, and S_{Cr} is serum creatinine. The creatinine clearance is normalized to BSA by multiplying by the factor 1.73/BSA in m^2. The relative constancy of creatinine production and its urinary excretion in the steady state helps one analyze for completeness of the collection (creatinine excretion/kg body weight). Urinary creatinine excretion should generally be 15–20 mg/kg/day in children over 3 years of age (20% higher than that for pubertal adolescent boys),[34–36] and values less than this indicate an incomplete urine collection, or loss of some urine. Daily variations in urinary creatinine excretion for a given subject can result in standard deviations of 10–15%.[37]

Creatinine clearance is derived from a 24-hour urine collection. On the day of the test, the child is asked to void and empty the bladder in the morning (7 a.m.), the urine is discarded, and the time noted as the start of the collection. All urine voided in the next 24 hours is collected in the container as part of this collection. At the end of 24 hours (7 a.m. on the next day), the bladder is emptied and the last void is deposited in the container as the final part of the collection. The volume of urine is noted accurately and the urine is analyzed for creatinine concentration. Blood (for serum creatinine) is drawn during the urine collections.

Averaging several short clearance periods (~30 minutes) after water loading tends to minimize errors in urine collection and improve supervision of the study.[38–40] Large variations in urinary creatinine excretion indicate significant vesicoureteral reflux or problems in bladder emptying that might warrant bladder catheterization to improve accuracy. In addition, creatinine concentration is affected to a small extent by dietary intake of meat, exercise, pyrexia, and a variety of substances. More importantly, it is well known that creatinine is secreted by the renal tubules and this secretory component accounts for ~10% of the urinary creatinine excretion in normal individuals.[40] This results in C_{Cr} exceeding C_{In}, particularly at low levels of GFR.[30]

Whereas in the steady state, creatinine production equals its excretion, creatinine production increases during growth and more than doubles from term infancy to adolescence.[34,41] The consequence of the increasing creatinine production is a steady increase in plasma creatinine as a function of age, along with a further increase with the increment in muscle mass in adolescent males (Figure 5.4).[42]

The administration of cimetidine to patients with renal disease causes a decrease in tubular creatinine secretion, resulting in a reduction in creatinine clearance that approximates the level of true GFR.[43] The protocol used by Hellerstein and colleagues used cimetidine for 3 days at a dose of 20 mg/kg in two divided doses (maximum of 1600 mg/day, and a sliding scale dose reduction for decreased GFR).[39] After an oral load of 7–8 ml/kg of fluids, urine was collected for four urinary clearance periods of ~30 minutes, urine output was replaced with water (ml-per-ml) during the test. Although the cimetidine protocol is a convenient and an inexpensive procedure for estimating GFR, severe vesicoureteral reflux, neurogenic bladders, and bladder dyssynergias can cause inaccuracies in the results.

Creatinine results from the enzymatic degradation of creatine synthesized in skeletal muscle. Urinary excretion of creatinine is therefore a product of muscle catabolism and hence an index of muscle mass.[36] In the steady state, serum creatinine also correlates well with muscle mass.[40,44] Creatinine has a MW of 113 Da, and is eliminated exclusively by the kidneys by glomerular filtration, and to a lesser extent by tubular secretion. Whereas urinary creatinine contributed by tubular secretion does not normally exceed 10%, this fraction rises greatly during chronic renal insufficiency, and creatinine clearance may greatly exceed GFR.[40] Diffusion of creatinine into the gut with subsequent catabolism may also interfere with the accuracy of its clearance in uremic patients.[45]

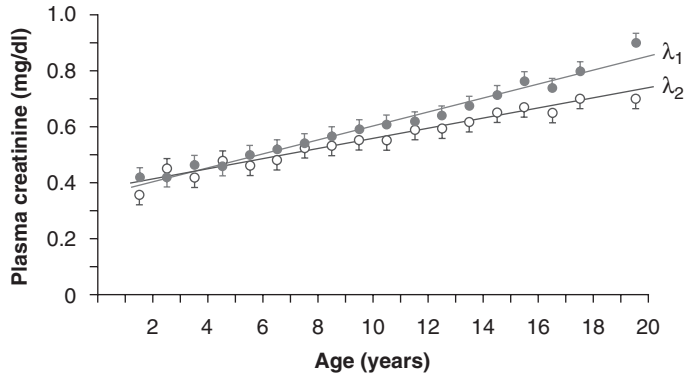

Figure 5.4 Serum creatinine as a function of age in males (closed circles) and females (open circles) with 1 standard error estimate, taken from 772 males and 626 females. Creatinine was measured using a modification of the Technicon Autoanalyzer Jaffe assay. (Reprinted from J Pediatr, 88, Schwartz GJ et al, Plasma creatinine and urea concentration in children: normal values for age and sex, 828, 1976. With permission from Elsevier.)

Estimated GFR based on serum creatinine

The close relationship between creatinine clearance and GFR on the one hand, and creatinine production and muscle mass on the other, along with the difficulties of collecting urine, have led to the concept of estimating GFR from serum creatinine and some parameter of body habitus, as detailed by Schwartz et al:[46]

$$eGFR = kL/S_{Cr}$$

where eGFR is estimated GFR in ml/min/1.73 m^2, k is a constant determined empirically by Schwartz and associates,[41] L is height in centimeters, and S_{Cr} is serum creatinine in mg/dl. This formula is also based on the relationship that C_{Cr} is reciprocally proportional to the serum creatinine. A dimensional analysis of k (mg creatinine/100 min × cm × 1.73 m^2) indicates that k is equal to $U_{Cr}V/L$, which is directly related to urinary creatinine excretion, which is in turn proportional to lean body mass.[34,41]

The value of k is 0.45 for term infants during the first year of life,[34] 0.55 for children and adolescent girls,[46] and 0.7 in adolescent boys.[35] Such a formula generally provides a good estimate of GFR (r = ~0.9) when compared with creatinine and inulin clearance data.[39,46] Interestingly, at high values of GFR, the variation between inulin clearance and GFR estimated by Schwartz formula was about 20%, but it was much smaller at lower levels of GFR.[39,46] There is no clear explanation for this finding. It should be noted that these constants were generated using creatinines measured using a modification of the Technicon Autoanalyzer method, which relies on a modification of the Jaffe chromogen reaction to determine creatinine. No formulae relating GFR to plasma creatinine determined enzymatically, using the creatinase methods available in more modern autoanalyzers, have been developed so far. Whereas enzymatic creatinine appears to agree with 'true' creatinine obtained

from the Jaffe reaction after Fuller's earth absorption, some manufacturers use calibration factors (bias) to produce Jaffe-comparable results.[47] This bias is not linear and is, therefore, unlikely to improve the accuracy of serum creatinine determination in children. Without the bias, the enzymatic creatinine measurements generally run 10–20% lower than those measured by the Jaffe method,[48] and so one would anticipate that 'k' values should be comparably smaller than those listed above.

Counahan and colleagues generated a similar formula using 'near-true' creatinine determinations, and the resulting k was 0.43.[49] The lower k value may reflect the lower value of creatinine after removal of non-creatinine chromogen with an ion exchange resin. Indeed, this k value is approximately 20% lower than the k obtained from the modified Technicon Autoanalyzer, which is in keeping with the expected reduction in apparent serum creatinine concentration using the 'true' method. It is important to point out that the estimated GFR values in the above study were compared with GFR determinations using the plasma disappearance of ^{51}Cr-EDTA (ethylenediaminetetraacetic acid), a method that accurately measures GFR.[50] However, in generating the relationship, five adults and some infants were included, leading to some heterogeneity of the sample.

The estimated GFR formulae have some limitations and should not be used in cases of severe obesity or malnourishment or limb amputation, in whom body height may not accurately reflect muscle mass.[41] Additionally, these GFR estimate formulae are not accurate when GFR is rapidly changing, such as in critically ill children, or in acute renal failure.[51]

The Cockcroft–Gault equation,[52] which is used to estimate GFR in adults, may also be useful in children over 12 years of age:[53]

$$\text{e'GFR} = (140 - \text{age})\ (\text{body weight in kg})/(72 \times S_{Cr})$$

where e'GFR is the estimated GFR using the Cockcroft–Gault equation in males; in females a correction factor of 0.85 is used. Whereas there is good overall agreement with standard inulin clearances in children, the correlation with GFR is not as good as with the Schwartz estimate and the scatter appears larger.[53] The adult formula, generated by the Modification of Diet in Renal Disease (MDRD) group, is not useful in children.[53]

Cystatin C

Cystatin C is a non-glycosylated 13 kDa basic protein that acts as a cysteine proteinase inhibitor, and is produced at a relatively constant rate. This constancy is apparently not influenced by presence of inflammatory conditions, muscle mass, gender, body composition, and age (after 12 months).[54,55] Blood cystatin C level is approximately 1 mg/L in healthy individuals.[56] Cystatin C is catabolized and almost completely reabsorbed by renal proximal tubular cells, so that little is excreted in the urine,[57] and cannot be used to calculate GFR. Interindividual variation of cystatin C level is significantly less (25%) compared with creatinine (93%).[58] The upper limit of the population reference interval for cystatin C is seldom more than 3–4 SD from the mean value of any healthy individual (compared with 13 SD for creatinine). These findings suggest that cystatin C is potentially a better marker than creatinine for detecting impaired renal function.

From a number of clinical studies of cystatin C,[59] including one in normal children,[54] two key findings are evident:

- the concentration of serum cystatin C correlated better with directly measured values for GFR than serum creatinine
- subtle decrements in GFR are more readily detected by the determination of serum cystatin C than by creatinine concentration.[59]

Thus, while cystatin C is not a conventional marker of GFR, reciprocal values of serum cystatin C levels are reasonably well correlated with GFR in adults[60,61] and in children.[48,62–64]

Whereas in some studies the serum concentration of cystatin C may be superior to serum creatinine in distinguishing normal from abnormal GFR,[65] a definitive numerical estimated GFR cannot be derived from its plasma concentration.[62] Furthermore, because it is metabolized and not excreted, cystatin C cannot be used to measure GFR by standard clearance techniques.[59] Other studies have shown that plasma cystatin C is slightly better than plasma creatinine in diagnosing renal insufficiency, but is less sensitive than creatinine clearance or eGFR (from kL/S_{Cr}).[66] Moreover, cystatin C levels may overestimate GFR in renal transplant patients.[67] More recent studies have shown that factors other than renal function, such as C-reactive protein (CRP) and smoking status, may influence serum cystatin C levels, so that caution must be used when interpreting serum cystatin C level as a measure of renal function.[68] The findings of cystatin C in the urine during glomerular and tubular injury also cast some doubt on the ability of serum cystatin C to accurately estimate GFR.[69,70] Indeed, Hjorth et al questioned whether any estimate of GFR can replace a clearance study.[71]

Single-injection clearance techniques

The renal clearance of a substance that is not metabolically produced or degraded, and that is excreted from the body completely or almost completely in the urine, can be calculated from compartmental analysis by monitoring its rate of disappearance from the plasma following a single intravenous injection.[72] The mathematical model for the disappearance curve is an open two-compartment system. The GFR marker is injected in the first compartment, equilibrates with the second compartment, and is excreted from the first compartment by glomerular filtration. Initially, the plasma concentration falls rapidly but at a progressively diminishing rate, as there is diffusion of the marker in its distribution volume as well as its renal excretion. Thereafter, the slope of the decline of plasma concentration predominately reflects its renal excretion rate. This latter decrease occurs at the same exponential rate in the compartments wherein it is distributed.

Indeed, the plasma disappearance curve can be resolved into two exponential decay curves by plotting the log of the plasma

concentration as a function of time and applying the technique of curve stripping (Figure 5.5). The terminal slow (renal) portion of the curve is extrapolated back to zero time, and its y-axis intercept (A) and slope (α) are determined. When the values along line A are subtracted from the original curve, a second log-linear function (line B) is obtained. Its y-axis intercept (B) and slope (β) are also noted. The clearance of the substance (GFR) can be calculated as:[72]

$$GFR = Dose \times 0.693/[(\exp(A)/\alpha + (\exp(B)/\beta)]$$

where Dose is the administered amount of GFR marker, and GFR is normalized to 1.73 m^2 by multiplying by 1.73/BSA. Thus, to obtain an accurate plasma disappearance curve, several blood samples are required. Extension of sampling to 5 hours is essential to assure accuracy at low levels of GFR.

Excellent and comparable results may also be obtained using the one-compartment (renal curve) model, by which samples are obtained 2–5 hours after injection, as described by Brochner-Mortensen:[73]

$$GFR = C1 \times GFR(A) + C2 \times [GFR(A)]^2$$

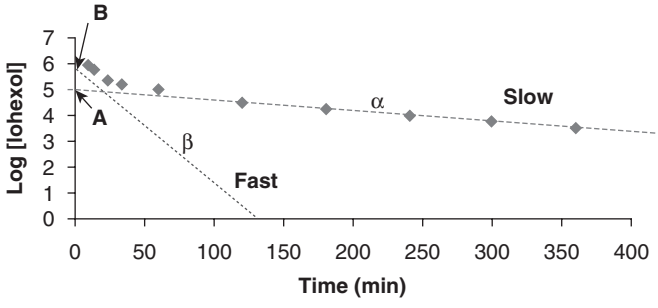

Figure 5.5 Disappearance of iohexol as a function of time after injection into the blood. The natural log of the iohexol concentration is plotted against the time in minutes. The curve can be stripped into two components: the slow or renal curve with slope α and intercept A. When those points are subtracted from the initial curve, a straight line with a steeper slope β defines the fast or distribution curve with intercept B.

where

$$GFR(A) = Dose/[\exp(A)/\alpha]$$

and C1 = 0.9908 and C2 = 0.001218, as generated by Brochner-Mortensen in adults by comparing to plasma disappearance curves for ^{51}Cr-EDTA.

DTPA, EDTA, and iothalamate

Historically, the plasma disappearance curve was most often used when assessing GFR with radionuclides (Table 5.5). DTPA (diethylenetriaminepentaacetic acid) has a MW of 393 Da and is excreted primarily by glomerular filtration. GFR can be measured in each kidney using a scintillation camera and the ^{98m}Tc-DTPA complex; however, the correlation with 24-hour creatinine clearances is only fair.[74] It should be noted that the plasma clearance of ^{99m}Tc-DTPA significantly exceeds the urinary clearance.[50,75] On the other hand, the plasma clearance of ^{99m}Tc-DTPA correlated well with the renal clearance of inulin.[50] Failure to accurately measure GFR may reflect the facts that the ^{99m}Tc can dissociate from the DTPA during the study, and there can be variations in protein binding, depending on the ligand attached to DTPA.[76] Some preparations with CaNa-DTPA gave results comparable to ^{51}Cr-EDTA, whereas others underestimated GFR by 7–22%.[76] Thus, the accuracy of ^{99m}Tc-DTPA may depend on the commercial source.

EDTA is another glomerular marker (MW = 292 Da) and is used as a chelate of ^{51}Cr, primarily in Europe. Its plasma clearance exceeds its urinary clearance by ~6 ml/min, particularly in patients with reduced renal function.[50] However, plasma clearance of ^{51}Cr-EDTA agrees well with that of renal inulin clearance,[50] indicating that it is a good marker for GFR. Values of ^{51}Cr-EDTA plasma clearances increase from birth to age 18 months and thereafter plateau (see Table 5.4B). The absolute numbers agree well with measurements performed using inulin clearances (see Table 5.4A).

Iothalamate sodium has a MW of 636 Da. It has been used as ^{125}I-radiolabeled or without radioactive label, its plasma concentration being measured by X-ray fluorescence, HPLC, or by

Table 5.5 Properties of markers of glomerular filtration

Property	Inulin	Creatinine	Iothalamate	DTPA	EDTA	Iohexol
MW (Da)	5200	113	636	393	292	821
Elimination half-life (min)	70	200	120	110	120	90
Protein binding (%)	0	0	<5	5	0	<2
Space distribution	ECW	TBW	ECW	ECW	ECW	ECW

ECW, extracellular water; TBW, total body water; DTPA, diethylenetriaminepentaacetic acid; EDTA, ethylenediaminetetraacetic acid.
Table adapted from Rahn et al.[88]

capillary electrophoresis. In a comparison of agents, the plasma clearance of ^{125}I-iothalamate was 13% higher than that of ^{51}Cr-EDTA.[77] The difference was reduced by pretreatment of the patients with probenecid, an organic anion secretory inhibitor. Extensive laboratory studies have shown unambiguously that iothalamate is actively secreted by renal proximal tubular cells, and may also undergo some tubular reabsorption.[77] The renal clearance of iothalamate significantly exceeds that of inulin in patients with normal renal function,[78] and any reported agreement with inulin clearance may reflect a fortuitous cancellation of errors between tubular excretion and protein binding.[79] Thus, iothalamate cannot be recommended as an ideal marker for measuring GFR.

Iohexol

A reliable alternative to inulin clearance avoids both the use of radioactivity and the problems related to timed urination and continuous infusion of the marker. Iohexol, a non-ionic, low osmolar, X-ray contrast medium (Omnipaque) that is safe and non-toxic and used for angiographic and urographic procedures, is eliminated from plasma exclusively by glomerular filtration.[80] Iohexol has a MW of 821 Da, a plasma elimination half-time of ~90 minutes, is distributed into the extracellular space, and has less than 2% plasma protein binding.[80,81] Iohexol is excreted completely unmetabolized in the urine with 100% recovery within 24 hours after injection.[82] Since iohexol can be quantified in small samples, capillary as well as venous sampling can be employed.[83] Extrarenal elimination of iohexol in a setting of reduced GFR is negligible.[84] Iohexol is measured in deproteinized plasma or serum by HPLC or X-ray fluorescence. The commercially available preparations contain two isomers of iohexol, both of which are handled similarly by the body.[83,85] In practice the major peak, eluting at about 5 minutes, is used for determining serum/plasma concentrations.[85] Most studies indicate close agreement between GFR (measured by inulin clearance) and clearance of iohexol, measured as standard renal clearance or plasma disappearance.[82,85–88] There is not only a very good correlation between plasma iohexol clearance and that of ^{51}Cr-EDTA but also no difference between the methods by Bland–Altman analysis.[89] Direct comparison with iothalamate indicates that the iothalamate clearance exceeds that of iohexol by 19%.[80]

Modeling of plasma disappearance of iohexol indicates that its excretion conforms to a two-compartment open system.[82,85] In a pilot study for the NIH (National Institutes of Health)-supported Chronic Kidney Disease in Children study (CKiDs), we have found that even with low GFR, serum iohexol concentrations decrease exponentially along the slow (renal) curve within 60–120 minutes of injection.[90] The clearance of iohexol (GFR) may also be calculated from the slow (renal) plasma disappearance curve (one-compartment system approximation beginning 120 minutes after injection) according to the method of Brochner-Mortenson (see above),[73] or by applying the Chantler correction, which assumes a constant correction factor of 0.87.[91,92]

It should be noted that the collection of urine without urinary catheters (using various methods to establish that the bladder is empty after voiding) does not add significant accuracy to the clearance estimate:[90,93] 24-hour urines may vary by as much as 10–15% from one day to another,[37] and a similar phenomenon can be seen when averaging multiple short urine collections. Therefore, a fair correlation with standard inulin clearance is perhaps the best that can be expected. The plasma disappearance of a marker that is excreted only by glomerular filtration may in fact be the gold standard that replaces the standard inulin clearance.

Determination of GFR by radionuclide scan

Estimation of GFR by use of radioisotopes is a commonly used technique in children, particularly with the limited availability of inulin and difficulties in collecting accurate timed urines in children. Commonly used radioisotopes are ^{99m}Tc-DTPA, ^{131}I- or ^{125}I-Hippuran, and ^{99m}Tc-MAG3 (mercaptoacetyltriglycine). Only the first compound is useful for GFR measurement. One method calculates GFR from the uptake of labeled tracer in each kidney and allows separate assessment of each kidney (split functions).[74] A second method utilizes the disappearance of the labeled marker from the plasma, and, as noted above, DTPA is variably accurate as a marker of GFR.

Hippuran is secreted and thus does not measure GFR, but provides information on renal blood flow; because of its protein binding, it is not as accurate as *p*-aminohippurate for this purpose. But hippuran has been used as a dynamic radionuclide renographic test of renal function that complements the predominantly anatomic information provided by most other imaging techniques. MAG3, because of its higher extraction ratio, which results in better renal images, has now supplanted hippuran for this purpose.[94]

Tests of tubular function

Unless there is a suspicion of specific transport defects (renal bicarbonate wasting, persistent acidosis, a concentrating defect, etc.), detailed evaluation of renal tubular functions is not routinely performed. Tests exploring specific functions of the renal tubules under conditions in which the tubule must develop an adaptive response may uncover disorders that are not readily apparent under basal conditions.

Renal bicarbonate handling

Renal regulation of acid–base balance requires the reclamation of bicarbonate that is filtered at the glomerulus, and this is primarily achieved by the proximal tubular function. Failure to reabsorb the filtered bicarbonate results in type II, or proximal renal tubular acidosis (PRTA), a well-known cause of failure to thrive in children. A second prominent tubular function is excreting protons and generating new bicarbonate in order to

replenish the bicarbonate pool in the body. This function is primarily attributable to the distal nephron, mostly in the cortical and medullary collecting ducts.

Detailed tubular acid–base handling can be studied by the bicarbonate titration test, which provides information about:

- renal threshold for bicarbonate
- the fraction of filtered bicarbonate that is reabsorbed in the kidney
- distal proton secretion.[95–97]

The bicarbonate titration test is usually conducted after determining that the urine pH is below 5.8, and therefore contains very little bicarbonate. At this point, the serum bicarbonate concentration should be below its renal threshold. A baseline sample of arterialized capillary blood or arterial blood is measured for bicarbonate, pH, and pCO_2. Then, an intravenous solution of 0.2–0.5 mol/L is infused at a rate that is anticipated to raise serum bicarbonate by ~2 mmol/L/h. Renal threshold for bicarbonate is reached when the urine pH of 6.5–7 is attained. This is confirmed by obtaining serum bicarbonate values at that point.

Renal threshold for bicarbonate

Edelmann et al defined the renal threshold for bicarbonate as the point at which there is significant urinary excretion of bicarbonate, which corresponds to a urine pH between 6.5 and 7.0.[97] Oetliker and Rossi regarded urinary pH above 6.8 as a criterion for renal threshold of bicarbonate.[98] Normal renal threshold for bicarbonate is 20–22 mmol/L in infants, 22–24 mmol/L in children, and above 24 mmol/L in adolescents. Threshold for bicarbonate is substantially reduced in PRTA.[79,99]

Fractional excretion of bicarbonate

Information related to the fraction of filtered bicarbonate excreted by the kidney is useful from both diagnostic as well as therapeutic perspectives. Measuring fractional excretion of bicarbonate (FE_{HCO_3}) at the time of the bicarbonate loading test requires determination of GFR. Although inulin can be employed as a marker in this test, endogenous creatinine clearance is usually adequate to estimate GFR and FE_{HCO_3}. The FE_{HCO_3} is calculated by using the formula:

$$U_{HCO_3}/S_{HCO_3} \times S_{Cr}/U_{Cr} \times 100$$

U_{HCO_3} is measured directly or determined from the Henderson–Hasselbalch equation:

$$pH = pK + \log (HCO_3^-/0.03 \times pCO_2)$$

where pK is corrected for cation concentrations from the formula:

$$6.33 - 0.5 \times \log \sqrt{\text{urine Na} + \text{K (mol/L)}}$$

Other parameters are measured in blood (sera) and urine, using conventional autoanalyzer methods.

The expected FE_{HCO_3} at a normal level of serum bicarbonate is less than 5%, which is also found in classical type I, or distal RTA (DRTA). FE_{HCO_3} of 15%, or higher, occurs in type II or proximal RTA, and a value of 5–15% is seen in type IV or hyperkalemic RTA. The information derived from calculation of FE_{HCO_3} at the normal level of serum bicarbonate threshold is helpful in planning appropriate bicarbonate therapy in a newly diagnosed child with RTA. Clearly, this test must be done without significant volume expansion, which is known to lower the serum bicarbonate threshold and raise FE_{HCO_3}, and hence the slow rates of infusion.

Urine – Blood pCO_2

In the setting of an alkaline urine (and a higher driving force) during bicarbonate loading, the secretion of protons in the distal nephron segment is favored. The secreted protons combine with filtered bicarbonate to generate carbonic acid. Because of limited carbonic anhydrase activity in the luminal side of the medullary collecting duct, the carbonic acid dehydrates very slowly into CO_2 and water.[95] This medullary trapping of CO_2 and the unfavorable surface-to-volume ratio of the lower urinary tract limits the diffusion of CO_2 out of the tubular lumen. Thus, the partial pressure of urinary CO_2 (U pCO_2) remains elevated with ongoing proton secretion, and this is used as a reliable index of distal nephron proton secretion.[96]

To study distal tubular proton secretion by urine–blood (U-B) pCO_2, the bicarbonate titration is further extended and the rate of infusion is doubled in order to produce a sufficiently alkaline urine. The U–B pCO_2, measured in the setting of an alkaline urine (pH > 7.5) is capable of detecting subtle defects of distal nephron acidification.[100,101] Normal U–B pCO_2 is > 20 mmHg.[101,102] U–B pCO_2 in DRTA is < 20 mmHg.

Tests of urinary acidification

Tests of proton secretory capability of the distal nephron are often necessary in the evaluation of a patient with metabolic acidosis and suspected RTA. Secreted protons are present free in solution (as determined by urine pH), or bound to two major urinary buffers, phosphate and ammonia. Titratable acid refers to the amount of alkali needed to raise the urine pH to 7.4. Net acid excretion equals the sum of titratable acid plus ammonium, minus bicarbonate.

Minimum urinary pH and net acid excretion

Renal proton excretion is tested by the urinary acidification test following an acid load. The acid load is usually given as oral ammonium chloride (dose 75–150 mEq/m^2) dissolved in lemon juice and sugar, or as enteric-coated capsules, and is ingested over 1 hour. This generally results in a state of moderate metabolic acidosis with blood pH below 7.33, and serum bicarbonate level below 16–18 mmol/L. Normal subjects lower urine pH below pH 5.5 and increase net acid excretion above 70 µEq/min per 1.73 m^2 (Table 5.6).[97,103] Patients with type I or DRTA

Table 5.6 Maturation of the renal response to an acute acid load in infants and children[a]

Age	UpH	Titratable acid	Ammonium	Net acid excretion
Pre-term (1–3 weeks)[1]	6.0 ± 0.1*	25 ± 4*	29 ± 2*	54 ± 6*
Pre-term (4–6 weeks)[1]	5.2 ± 0.4	36 ± 9	40 ± 8*	76 ± 13*
Pre-term (3–4 months)[2]	5.2 ± 0.2	54 ± 20	37 ± 10*	90 ± 24*
Term (1–3 weeks)[1]	5.0 ± 0.2	32 ± 8*	56 ± 9*	88 ± 8*
Infants (1–16 months)[3]	4.9 ± 0.1	62 ± 16	57 ± 14*	119 ± 30
Children (7–12 years)[3]	4.9 ± 0.2	50 ± 10	80 ± 12	130 ± 14

[a]Mean ± SD; minimum urine pH (UpH); maximal titratable acid, ammonium, and net acid excretion in timed urine collections given as μEq/min per 1.73 m^2. Acute acid load was NH_4Cl given orally at 3.9–5 mEq/kg (75–100 mEq per m^2) for infants and 5.4 mEq/kg (150 mEq per m^2) for children.
*Significantly different ($P < 0.05$) from values in children by Tukey's test.
Data compiled from the following references:
[1]Svenningsen NW. Pediatr Res 8:659, 1974
[2]Schwartz GJ et al. J Pediatr 95:102, 1979
[3]Edelmann CM Jr. et al. J Clin Invest 46:1309, 1967.

cannot decrease urine pH below 5.5, or increase net acid excretion above 70 μEq/min/1.73 m^2. In type II or PRTA, these levels are achieved once serum bicarbonate falls below the reduced renal threshold. Patients with type IV RTA have normal ability to decrease urine pH but defective excretion of ammonium and net acid.

A reliable screening tool for urinary acidification is to examine the pH of the second fasting urine of the morning. An acidified urine with a pH < 5.5 excludes incomplete or minor forms of distal RTA. However, the range of urine pH in early morning urine of normal children is 5.16–7.07, with a median pH of 6.0, clearly underlining low specificity of this screening test.[104] Children who cannot concentrate the urine may also be unable to adequately decrease urine pH. Similarly, in patients with decreased extracellular volume, the urinary acidification defect may be a result of lack of sodium within the lumen of the distal nephron. Other conditions causing high urine pH during metabolic acidosis include:

- urinary infections with urea-splitting organisms
- severe potassium depletion, which stimulates ammoniagenesis, and excess ammonia buffers all free luminal protons
- gastrointestinal losses producing avid salt retention with decreased distal sodium delivery, leading to an abnormal distal luminal electrochemical gradient and subsequent increased urinary pH.[105,106]

Therefore, it is important to also measure urinary sodium and osmolality, in addition to pH and ammonium, since a low pH associated with reduced ammoniuria does not exclude a defective distal acidification. Conversely, high ammoniuria may be responsible for the fact that urine pH does not decrease below 5.5.

Surrogate markers of renal ammonium generation

In many clinical laboratories it is difficult to measure urinary ammonium, and alternative tests have been suggested. Of these, urinary net charge (UNC, formerly known as urinary anion gap) provides a good estimation of urinary ammonia content.[105,107–109]

$$UNC = UNa^+ + UK^+ - UCl^-$$

A negative UNC is the appropriate response to chronic metabolic acidosis, indicating that urinary NH_4^+ is present. A positive value suggests a lack of urinary NH_4^+ and a defect in distal urinary acidification. The UNC cannot be used in high serum anion gap acidosis (because of excessive urinary organic anions), or in severe volume depletion with avid Na^+ retention (because of decreased distal Na^+ delivery). Caution should also be used in interpreting the UNC in neonates.[110]

If excessive unmeasured urinary anions are suspected, urinary ammonium concentration can also be estimated from the difference between measured and calculated urine osmolalities:[109,111]

$$\text{Urine } NH_4^+ = 0.5 \times (\text{Osmolality} - [2(Na^+ + K^+) + \text{urea}/2.8 + \text{glucose}/18])$$

where $[2(Na^+ + K^+) + \text{urea}/2.8 + \text{glucose}/18]$ is calculated osmolality in mOsm/kg and NH_4^+, Na^+, and K^+ are in mmol/L, and urea and glucose are in mg/dl. A value < 20 mOsm/kg is anticipated in a patient with distal RTA.

These tests help distinguish different forms of RTA. Patients with distal RTA are unable to both maximally decrease urinary pH and increase net acid excretion up to normal values. In proximal RTA, minimal urinary pH and normal net acid excretion are achieved once serum bicarbonate falls below the renal threshold. Patients with type IV RTA show normal ability to decrease urinary pH but defective excretion of ammonium.

Furosemide test

Furosemide increases distal sodium delivery, which generates an electronegative lumen potential and favors proton secretion. This principle has been used to test the distal tubular urinary acidification. After furosemide is administered (dose 1 mg/kg) intravenously or orally, within 2 hours a normal subject excretes urine with pH below 5.2, associated with a kaliuretic response. In 20 children given 1 mg/kg furosemide, Rodriguez-Soriano and Vallo reported the mean urine pH to be 4.96 and FE_K of 35.4%.[112]

Type I, or DRTA patients, with intrinsic defect in the proton pump cannot maximally decrease urine pH in response to furosemide. On the other hand, patients with type IV RTA, those with subnormal distal proton secretion secondary to low distal delivery of sodium (i.e. nephrotic syndrome), or reversible impairment of sodium distal reabsorption (i.e. sickle cell anemia or lithium administration) respond normally.

Acetazolamide test

Acetazolamide inhibits carbonic anhydrase, reduces proximal reabsorption of bicarbonate, and thereby causes bicarbonaturia and an alkaline urine. Oral acetazolamide is given at a dose of 15–20 mg/kg and pCO_2 is measured in blood and urine. A normal response shows an increase in urine pCO_2, and a U–B $pCO_2 > 20$ mmHg, suggestive of increased proton secretion. Children with primary defects of the distal proton pump do not increase urine pCO_2. This test gives results similar to those from patients subjected to bicarbonate loading.[113]

Test for renal glucose handling

Glucose is reabsorbed in the proximal tubule. Below a threshold level, all filtered glucose is reabsorbed and there is none in the urine. Once the filtered glucose load saturates the transport systems, the maximum rate of reabsorption is attained. From that point on, the urinary glucose elimination parallels the filtered load. To test the proximal tubular reabsorption of glucose the patient should be in the fasting state so that the urine is free of glucose. A water load is given (5 ml/kg). The titration curve can be obtained by infusing a 30% glucose solution at progressively increasing flow rates.[114] The starting rate of infusion is 1.6 ml/m^2/min. After a 20-minute equilibration period, two or three 15-minute collections of urine are obtained. Serum samples are obtained at the midpoint of each urine collection period. Accurate urine collections may require bladder catheterization in young children.

The normal serum glucose threshold is 180 mg/dl, and the maximum tubular reabsorption of glucose normalized to 1.73 m^2 BSA averages 213 ± 73 mg/min and 362 ± 96 mg/min for infants aged 2.5–24 weeks and children aged 1.5–13 years, respectively.[115] When normalized to GFR, there is no difference in maximum tubular glucose reabsorption (294 ± 74 mg/dl GFR) for infants and (283 ± 47 mg/dl GFR) for children.[115]

Maximal urinary concentrating ability

The simplest method to examine urinary concentrating capacity is to measure urinary osmolality after an overnight fluid restriction. If diabetes insipidus is suspected, water deprivation should be performed under careful observation over a period of 6–8 hours because of a significant risk of dehydration. A loss of 3% of body weight indicates that the test should be terminated. If the weight loss is less than 3%, the patient can usually tolerate the rigors of overnight thirsting.

A normal noon meal is given the day of the test, following which, except for a dry evening meal, the child does not ingest water or food until the test is completed. The bladder is emptied at bedtime and all urine passed from bedtime to 7 a.m. is pooled as an overnight collection. Two subsequent urines are also collected for osmolality. Urinary osmolality increases after 12 hours of water deprivation. In healthy children above 2 years of age the mean values of urinary osmolality in the first and second urine samples voided after the overnight collection are > 1000 mOsm/kg water (Table 5.7).[1,116] Infants during the first month of life concentrate the urine to about 60% that of older children. However, infants are able to increase urinary osmolality to mature levels by ingesting a very high (8 g/day/kg) protein diet and restricting fluids to 120 ml/kg.[117]

In the absence of heavy proteinuria or radiocontrast material in the urine, the osmolality can be estimated from urine specific gravity by multiplying the last two digits of the refractometric measurement by 40.[1] For example, specific gravity of 1.027 corresponds to osmolality of 1080 mOsm/kg water, and signifies normal concentrating capacity.

In primary polydipsia, prolonged fluid restriction is hazardous because of an induced hypotonic medullary interstitium. In such cases, a progressive reduction in fluid intake over days to weeks is required before exposing the child to a concentrating test.

Table 5.7 Urinary concentrating capacity

Age	Urinary osmolality
7–40 days	657 ± 115[a]
2 months to 3 years	416 × log (age days) + 63 ± 145[b]
3–15 years	1069 ± 128[b]
2–16 years	1089 ± 110[c]

Mean ± SD; concentration capacity progressively increases up to age 3 years.
Data from the following references:
[a]Edelmann et al.[117]
[b]Winberg J. Acta Paediatr 48:318, 1959.
[c]Edelmann et al.[1]
Data from subjects in Reference[b] obtained from overnight thirst combined with intramuscular pitressin tannate.

Vasopressin stimulation

If a concentrating defect is demonstrated or suspected, the sensitivity of the kidney to exogenous antidiuretic hormone (ADH) should be examined. The agent most commonly used is 1-desamino-8-D-arginine vasopressin (desmopressin, DDAVP), which can be given intranasally at doses of 10 μg in infants and 20 μg in children.[116] In infants, the usual fluid intake is restricted by 50% in the 12 hours following DDAVP administration to prevent overhydration and hyponatremia. Osmolality is measured in individual urine samples over the 6–8 hours after DDAVP administration. Assessment of urinary concentration capacity by giving DDAVP at bedtime and collecting one urine sample the following morning yields a reliable and easy to perform result in children.[118]

Maximal urinary dilution ability

Water loading to induce maximal urinary dilution and suppression of aldosterone and vasopressin requires extracellular volume expansion. Maximal excretion of electrolyte-free water is generated in the diluting segment of the tubule and an indirect estimate of solute reabsorption in the different segments of the nephron may be obtained by calculating a variety of urinary indices, as shown in Table 5.8.[119]

Oral loading of water at 20 ml/kg is followed by a constant intravenous infusion of 0.45% saline (2000 ml/1.73 m^2), administered over 2 hours. Calculations are performed in the most dilute samples (urine osmolality < 70 mOsm/kg water) with the highest free water clearance. Each urine collection is factored by creatinine clearance (as an estimate of GFR). The free water clearance is calculated from the following equations:

$$C_{Osm} = U_{Osm}/S_{Osm} \times V$$

and

$$C_{H_2O} = V - C_{Osm}$$

where V is the urine volume in ml/min, U_{Osm} and S_{Osm} are urine and serum osmolalities, and C_{Osm} is the osmolar fractional clearance in ml/min, and these are factored by 1 dl of glomerular filtrate (GF). This test can localize the site of defective reabsorption in tubular disorders, such as in Bartter syndrome characterized by excessive loss of sodium, potassium, and chloride. Clearances of sodium, potassium, and chloride are performed similarly using the formula:

$$C_x = U_x/S_x \times V$$

where V is urine flow in ml/dl of glomerular filtrate. Whereas the computed indices in Table 5.8 can provide useful information about tubular transport based on theoretical assumptions, some caution should be used in interpreting such tubular data derived from clearance methodology.

Table 5.8 Normal urinary excretion indices in infants and children undergoing maximal free water clearance

Parameter	Infants	Children
Urine osmolality (mOsm/kg water)	51.8 ± 12.8	54.1 ± 13.3
Urine volume (ml/dl GF)	22.8 ± 3.6	17.2 ± 2.7*
Osmolar clearance (ml/dl GF)	4.3 ± 1.3	3.2 ± 0.7*
Free water clearance (ml/dl GF)	18.5 ± 2.9	14.0 ± 2.6*
Sodium clearance (ml/dl GF)	1.9 ± 0.8	1.4 ± 0.4*
Potassium clearance (ml/dl GF)	19.9 ± 12.0	12.9 ± 5.2*
Distal delivery (water + sodium, ml/dl GF)	20.4 ± 2.9	15.3 ± 2.6*
Percentage of sodium reabsorbed distally (%)	90.8 ± 4.5	90.9 ± 3.3
Creatinine clearance (ml/min/1.73 m^2)	88.5 ± 27.1	124.8 ± 25.2*

Data are mean ± SD; *significantly different from infants ($p < 0.05$).
Data obtained at peak values of sustained water diuresis, resulting from an oral water load of 20 ml/kg over 30 minutes plus 0.45% saline at 1000 ml/h/1.73 m^2 over 2 hours.
Free water clearance, C_{H_2O} = volume − osmolar clearance, provides an estimate of sodium reabsorption by the diluting segments.
Distal delivery = free water clearance + sodium clearance. In the absence of bicarbonaturia or hyperkaliuria, distal delivery is nearly identical when using sodium or chloride clearance.
Percentage of sodium reabsorbed distally = free water clearance/(free water + sodium clearances).
GF, glomerular filtrate; GFR is approximated by endogenous creatinine clearance.
Standard clearance formula: $C_x = U_x \times V/P_x$ and is corrected to glomerular filtrate or 1.73 m^2 BSA (body surface area).
Reproduced with permission from Rodriguez-Soriano et al.[119]

Urinary solute excretion

The kidney controls the homeostasis of a variety of electrolytes. Most of these solutes are freely filtered and either secreted or reabsorbed by the tubules. The urinary excretion of such solutes reflects such tubular transport functions of the kidney. The following section briefly summarizes the normal handling of a variety of such electrolytes.

Sodium, chloride, and potassium

On a normal Western diet, children excrete approximately 3–4 mmol/kg/day of sodium. Water and salt homeostasis requires independent regulation of sodium and water, because of variability in the intake. Urinary sodium concentration is dependent on the degree of concentration or dilution of urine. For this reason, the excretion of urinary solutes is frequently normalized to that of creatinine. Under conditions of severe volume contraction, sodium can be undetectable in the urine. Normal sodium/creatinine ratios are given in Table 5.9. The handling of sodium is often expressed as a fractional excretion rate. The fractional excretion of sodium (FE_{Na}) is calculated as:

$$FE_{Na} = \frac{U_{Na}/S_{Na}}{U_{Cr}/S_{Cr}}$$

FE_{Na} in normal individuals ranges from 0.3 to 1.6%, depending on salt intake.[120] In patients with prerenal azotemia, FE_{Na} is less than 1%, whereas it is above 3% in acute tubular necrosis.

Chloride is handled similarly to sodium. The measurement of urinary chloride is useful in the diagnosis of metabolic alkalosis. A urinary chloride above 10 mmol/L indicates metabolic alkalosis of renal origin, whereas lower concentrations of urinary chloride suggest volume contraction as the cause of metabolic alkalosis.

Urinary potassium excretion is approximately 1–2 mmol/kg/day and is primarily regulated in the distal nephron, under the influence of aldosterone and by the amount of salt and water delivered to the distal nephron. The renal ability to conserve potassium is not as effective as for sodium. Therefore, urinary potassium excretion does not decrease to < 15 mmol/L. Normal potassium/creatinine ratios are shown in Table 5.9. Normal FE_K in children ranges from 10 to 30%.[99]

To estimate the action of aldosterone on the distal nephron, one can calculate the transtubular potassium concentration gradient (TTKG):

$$TTKG = \frac{U_K/S_K}{U_{osm}/S_{osm}}$$

The TTKG is > 5 in the presence of normal aldosterone action and decreases to < 3 in the absence of mineralocorticoid activity or secretion of potassium into the distal nephron.[112] The TTKG rises > 11 with a potassium load, indicating increased potassium secretion.

Calcium, phosphate, and magnesium

Urinary calcium excretion is often examined as a cause of hematuria and kidney stones. Urinary excretion of calcium is dependent on dietary intake as well as age (see Table 5.9), being higher in infants.[121,122] In a southern Italian study, the urinary excretion of calcium was 3–4 mg/kg/day in children aged 3–5 years and decreased to 1.5–2.5 mg/kg/day in children aged 15–16 years.[123] In children > 5 years of age, hypercalciuria

Table 5.9 Age-dependent 5th and 95th percentiles for urinary solute/creatinine ratios

	Age (years)															
	0.1–1		1–2		2–3		3–5		5–7		7–10		10–14		14–17	
Solute/Cr (mol/mol)	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%	5%	95%
Na/Cr	2.5	54	4.8	58	5.9	56	6.6	57	7.5	51	7.5	51	6	34	–	28
K/Cr	11	74	9	68	8	63	6.8	48	5.4	33	4.5	22	3.4	15	–	13
Ca/Cr	0.09	2.2	0.07	1.5	0.06	1.4	0.05	1.1	0.04	0.8	0.04	0.7	0.04	0.7	0.04	0.7
P/Cr	1.2	19	1.2	14	1.2	12	1.2	8	1.2	5	1.2	3.6	0.8	3.2	0.8	2.7
Mg/Cr	0.4	2.2	0.4	1.7	0.3	1.6	0.3	1.3	0.3	1	0.3	0.9	0.2	0.7	0.2	0.6
Ox/Cr	0.06	0.2	0.05	0.13	0.04	0.1	0.03	0.08	0.03	0.07	0.02	0.06	0.02	0.06	0.02	0.06
Ur/Cr	0.75	1.55	0.5	1.4	0.47	1.3	0.4	1.1	0.3	0.8	0.26	0.56	0.2	0.44	0.2	0.4

Cr, creatinine; P, phosphate; Ox, oxalate; Ur, urate. For conversion to mg units: 1 mmol = 113 mg Cr; 23 mg Na; 39 mg K; 40 mg Ca; 32 mg P; 24 mg Mg; 90 mg Ox; 168 mg Ur.

Adapted from the following references:

- Guignard and Santos.[79]
- Matos et al.[128]
- Matos et al.[121]

is usually defined as the excretion of more than 4 mg/kg/day, or a urine calcium (mg)/creatinine (mg) ratio above 0.2 .[124,125]

Urinary phosphate excretion decreases with maturation (see Table 5.9).[126] Older children normally excrete 15–20 mg/kg/day, compared with 35–40 mg/kg/day in young children.[123] After age 4, the fractional excretion of phosphate is approximately 7 ± 3%.[126]

Urinary magnesium excretion also shows a maturational decrease, as shown by the magnesium/creatinine ratios (see Table 5.9). Older children excrete 1.5–2.0 mg/kg/day, compared with 2.3–2.6 mg/kg/day in younger children.[123] The FE_{Mg} is normally about 5%, but decreases to < 1% in the setting of magnesium deprivation.[127]

Uric acid, oxalate, and citrate

Elevated concentrations of uric acid and oxalate and low levels of urinary citrate are also risk factors for the development of kidney stones. Both oxalate and uric acid show maturational decreases in urinary excretion (see Table 5.9).[128–130] Uric acid excretion decreases from 10–20 mg/kg/day in 3–5-year-old Italian children to 5–10 mg/kg/day in older children.[123] Brazilian children show a decrease from 5–15 mg/kg/day in preschoolers to 4–10 mg/kg/day in adolescents.[19] Hyperuricosuria is also diagnosed by examining urinary uric acid concentration factored by creatinine clearance ($U_{urate} \times S_{creat}/U_{creat}$, each in mg/dl); hyperuricosuria is defined by a value > 0.54–0.56 mg/dl of glomerular filtrate.[125,131] Alternatively, hyperuricemia is defined as the excretion of uric acid above 815 mg/24 hours/1.73 m^2.[132]

Urinary oxalate excretion was 1–2 mg/kg/day in Italian children aged 3–5 years old and decreased to 0.3–0.7 mg/kg/day in older children.[123] Table 5.9 shows the decrease in urinary oxalate/creatinine ratios with age.[128] Hyperoxaluria is also defined as urinary oxalate exceeding 0.5 mmol (45 mg)/24 hours/1.73 m^2, or 0.048 mg oxalate/mg creatinine (0.06 mol/mol) in children older than 5 years of age.[128]

Urinary citrate excretion normally averages 0.03 mmol (6.3 mg)/kg per 24 hours.[133] The range of urinary excretion of citrate does not show maturational changes, but it is clear that females excrete more urinary citrate than males.[134] Hypocitraturia predisposes to kidney stone formation. Hypocitraturia is defined as a urinary citrate/creatinine ratio < 300 mg/g (0.176 mol/mol) in girls and 128 mg/g (0.074 mol/mol) in boys.[134]

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6 Diagnostic imaging of the urinary tract

Dorothy Bulas, Bruce Markle, and Eglal Shalaby-Rana

Radiologic imaging plays a vital role in the evaluation of the urinary tract in children. Multiple imaging modalities are available for the diagnostic work-up of renal disorders in children. Ultrasonography is particularly useful in the evaluation of the structure of the kidneys and bladder without the use of ionizing radiation. Fetal ultrasound examination has been instrumental in the identification of urologic abnormalities long before they become clinically evident. Computed tomography (CT) as well as magnetic resonance imaging (MRI), with their excellent spatial resolution, are useful in the evaluation of the kidneys and vascular structures. These imaging modalities are often complementary, each with their clinical indications and applications, as well as limitations.

Conventional radiology

Conventional imaging techniques include the KUB (Kidneys, Ureter, Bladder) X-ray, the intravenous pyelogram (IVP), and the voiding cystourethrography (VCUG). The KUB is used to assess for the presence of calculi along the urinary tract, as well as examine the spine for dysraphism. IVP has largely been replaced by nuclear medicine techniques and its indications in clinical use in children are only few. In the past, IVP has been used in the evaluation of hydronephrosis, calculi, and complicated duplex collecting systems and has been replaced by a combination of ultrasonography, nuclear medicine, CT, and MRI.

Voiding cystourethrography

The VCUG is primarily indicated for detection of vesicoureteric reflux (VUR), and for delineating anatomy of the urinary bladder and urethra.

Technique

The VCUG needs no specific patient preparation. After the initial scout KUB is taken, using sterile technique, the bladder is catheterized with a feeding tube. Presence of parents in the procedure room and using water-soluble topical anesthetic gel may facilitate the procedure in an apprehensive child. Radioiodinated contrast (Cystoconray) is instilled into the bladder under gravity drip. The approximate volume of the radiocontrast to be used can be calculated by the formula:

$$\text{Bladder volume (ml)} = (\text{Age in years} + 2) \times 30$$

An initial filling film is taken to evaluate for bladder-filling defects, such as ureterocele, which may be obscured by a contrast-filled bladder. Signs of a full bladder should be observed in the patient during contrast instillation. These include slowing of the contrast drip, patient discomfort, and upturning of the toes. Images are taken of the full bladder, the ureterovesical junctions, the kidney fossae, and the urethra.

Complications of VCUG include urinary tract infection, chemical cystitis, vasovagal attack, and retrograde spread of infection leading to acute pyelonephritis. A urine culture is usually obtained during procedure and before withdrawal of the catheter.

Interpretation

The normal urinary bladder is a centrally placed smooth-walled globular structure. The urethral walls are smooth and the posterior urethra is visualized as a non-distended smooth-walled passage (Figure 6.1). Ectopic ureteroceles, which are frequently associated with duplex collecting systems, are seen as a filling defect low in the bladder in the early bladder-filling image (Figure 6.2). Bladder wall trabeculation (Figure 6.3) occurs as a result of functional (neuropathic bladder) or mechanical bladder outlet obstruction (posterior urethral valve). Diverticuli of the bladder can also be seen in the above clinical circumstance (Figure 6.4). Posterior urethral valves seen in males show a dilated posterior urethra and obstructed flow of contrast below the level of the valves (Figure 6.5).

Classification of VUR

Vesicoureteral reflux, if present, can be classified into five grades according to the International System of Grading (Table 6.1).[1] Intrarenal reflux may be seen with grades IV and V reflux. Reflux into duplex collecting systems, usually into the lower pole moiety, can be detected with its more inferior and lateral placement, the 'drooping lily' sign (Figure 6.11).

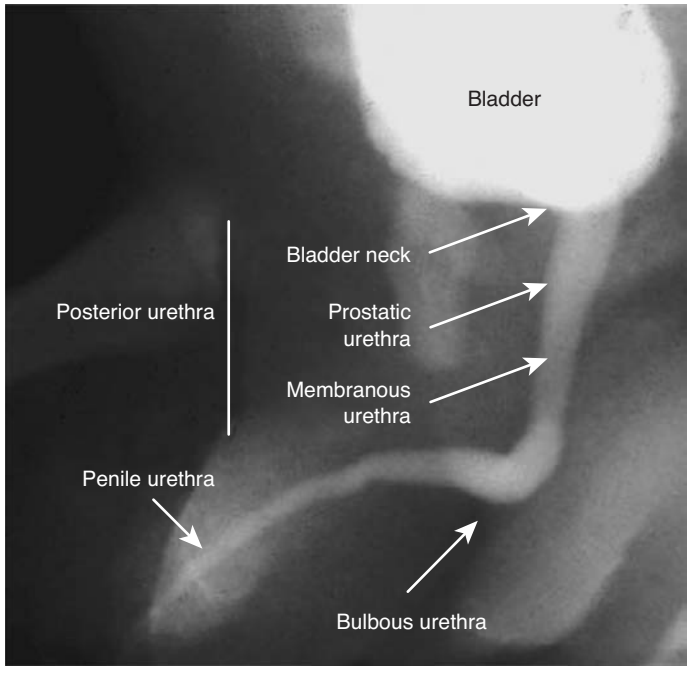

Figure 6.1 Contrast VCUG showing normal radiologic anatomy in male urethra.

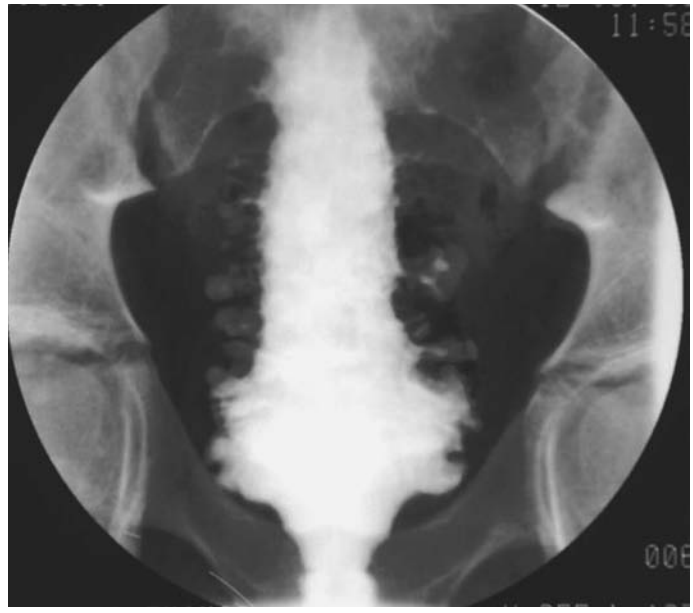

Figure 6.3 Contrast VCUG in a patient with long-standing bladder outlet obstruction. Severely trabeculated bladder with a narrow lumen, the so-called 'Christmas tree' appearance is evident.

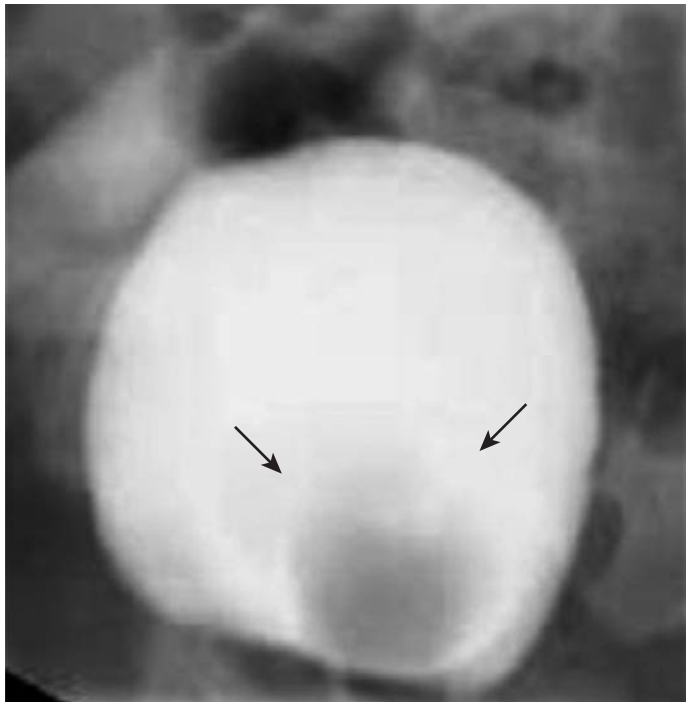

Figure 6.2 Contrast VCUG showing a ureterocele (arrows).

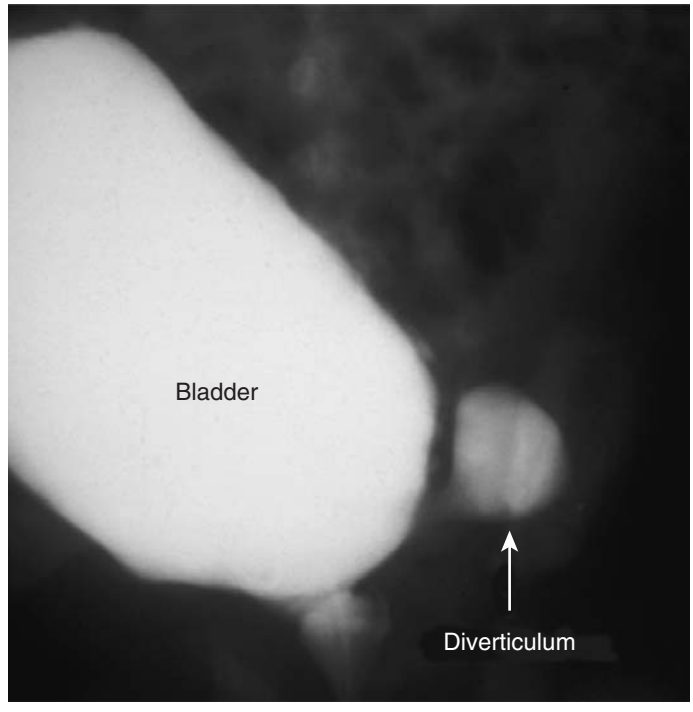

Figure 6.4 Contrast VCUG demonstrating a bladder diverticulum.

Renal ultrasound

Ultrasound is an ideal modality for the evaluation of the genitourinary system of the fetus, children, and adults. It is a minimally invasive procedure that is inexpensive, uses no radiation, requires no sedation, can assess organs in multiple planes, and can evaluate arterial and venous flow with the use of Doppler ultrasound. Ultrasonography can evaluate renal size, position, anatomy, urinary bladder masses, anomalies, and pre- and postvoid bladder volume and function. Ultrasound is useful

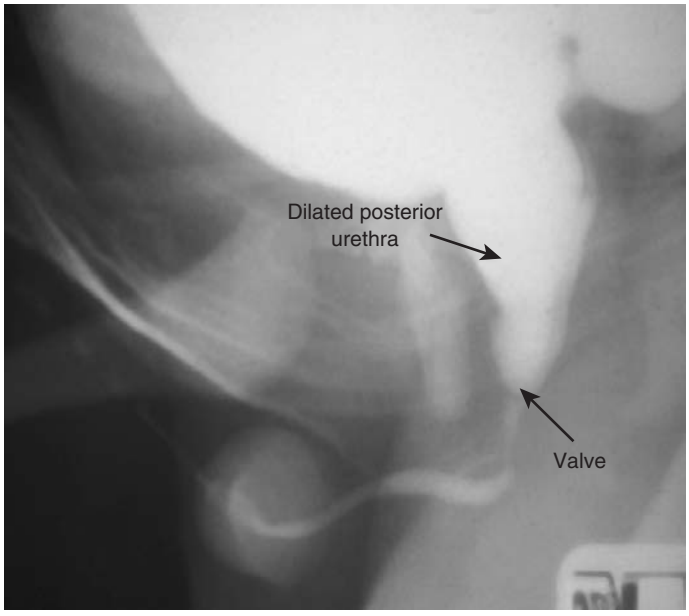

Figure 6.5 Contrast VCUG showing posterior urethral valves. Marked dilatation of the prostatic urethra with focal narrowing in the distal posterior urethra (arrow), due to the valve.

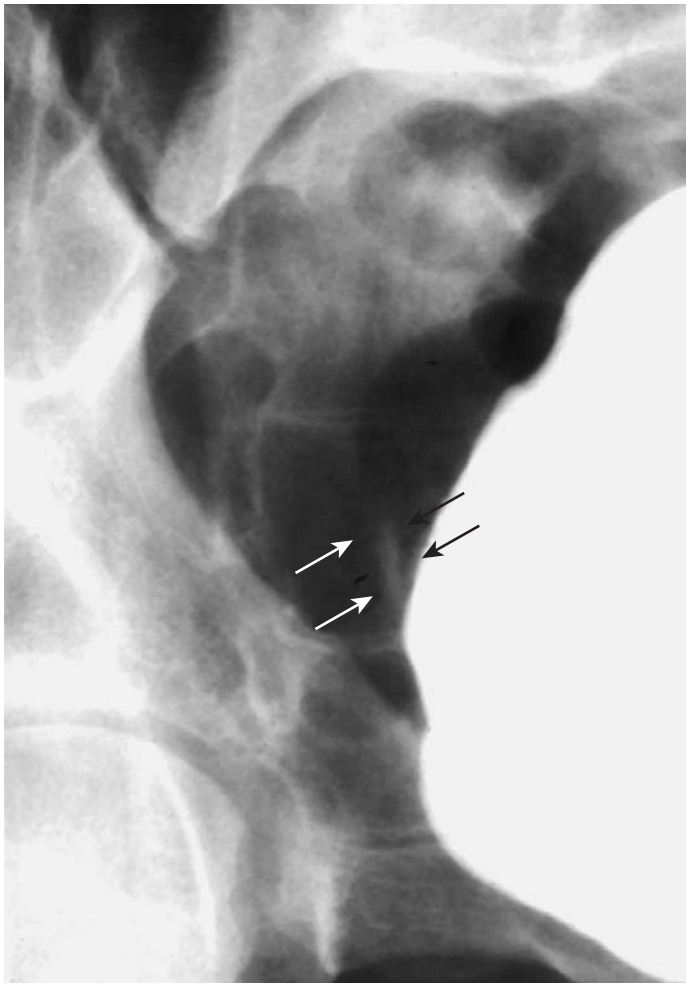

Figure 6.6 Contrast VCUG demonstrating grade 1 vesicoureteric reflux (arrows).

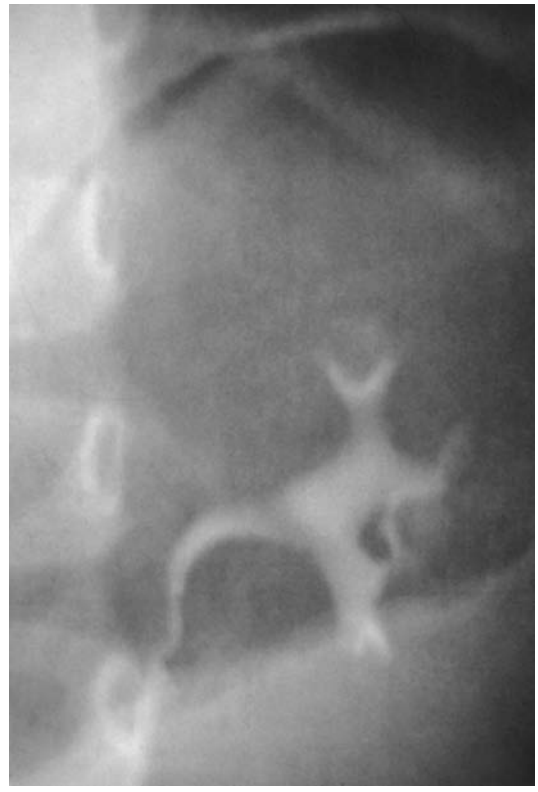

Figure 6.7 Contrast VCUG demonstrating grade II vesicoureteric reflux. The calyces are sharp with deep papillary impressions.

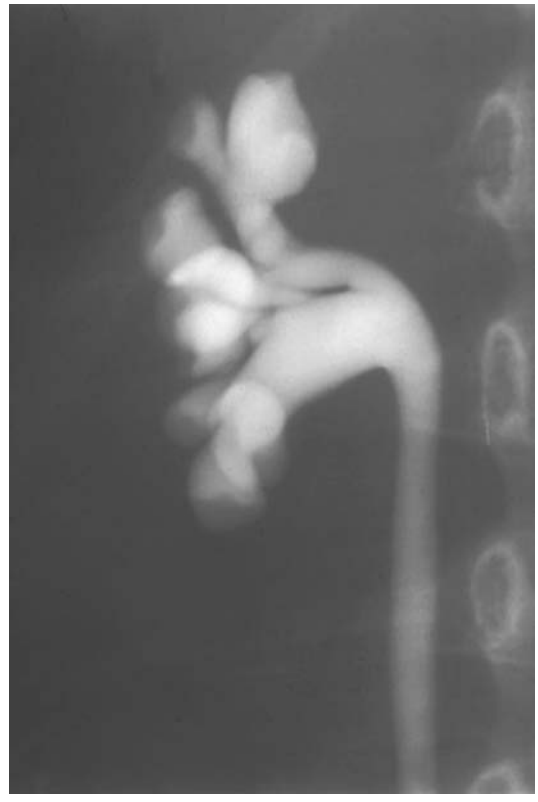

Figure 6.8 Contrast VCUG showing grade III vesicoureteric reflux. Calyces blunted but papillary impressions are preserved.

Table 6.1 Grading of vesicoureteric reflux	
Grade I:	Reflux into the ureter only (Figure 6.6)
Grade II:	Reflux into the collecting system, without blunting of calyces (Figure 6.7)
Grade III:	Reflux into the collecting system, with mild blunting of calyces and preservation of papillary impressions; ureter may be mildly dilated (Figure 6.8)
Grade IV:	Reflux into the collecting system, with moderate blunting of calyces, some loss of papillary impressions, and occasional complete loss of papillary impressions (clubbing); ureter dilated and tortuous (Figure 6.9)
Grade V:	Clubbing of most of calyces. Ureter is dilated and tortuous (Figure 6.10)

From Lebowitz et al.[1]

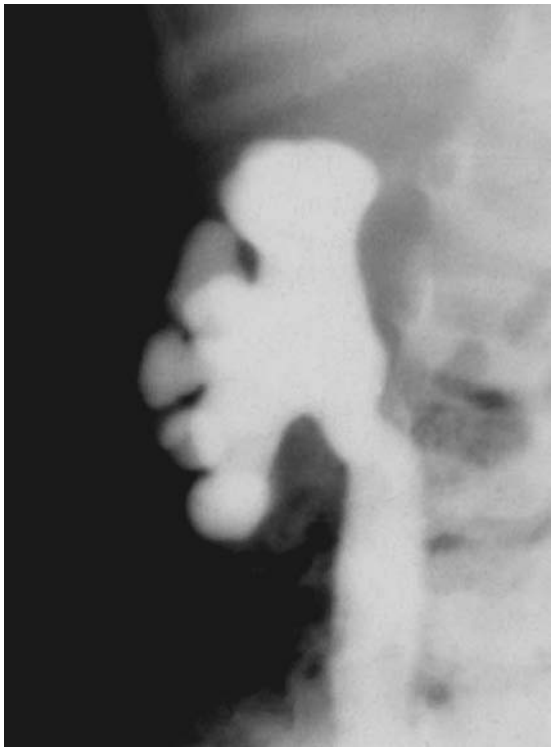

Figure 6.9 Contrast VCUG demonstrating grade IV vesicoureteric reflux. Calyces are significantly blunted with very shallow papillary impressions. Ureter is also dilated.

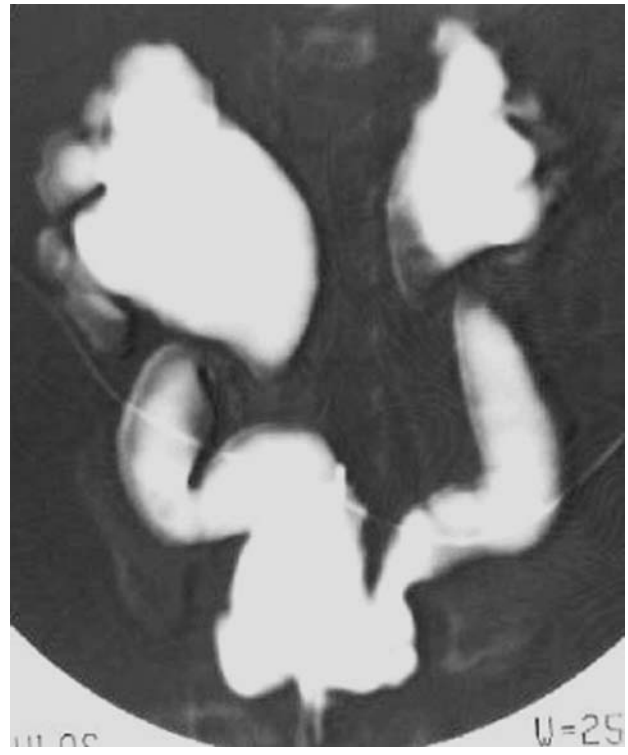

Figure 6.10 Contrast VCUG demonstrating grade V vesicoureteric reflux. Note dilated and tortuous ureters, along with clubbing of most calyces.

for the evaluation of structures around the urinary tract that may obstruct the kidney and bladder. Ultrasound is also used in the guidance of percutaneous procedures such as renal biopsies or drainages.

Limitations of ultrasound include the inability to penetrate gas or bone. Crying infants and obese patients may also restrict resolution. It also needs to be pointed out that the recorded observations of ultrasound are highly operator-dependent. Despite these limitations, ultrasound is a cornerstone in the evaluation of renal and bladder anatomy.

Renal size

Evaluation of the kidney begins with an assessment of size. Normal data for renal size are available prenatally through adolescence (Table 6.2). Graphic representation of renal size in relation to age and height is shown in Figure 6.12. Table 6.3 lists the causes of abnormal kidney size.

Evaluation of renal architecture

Location and configuration of the kidney is important in the identification of pelvic, horseshoe, and duplex kidneys. Renal

Figure 6.11 Vesicoureteric reflux into the lower pole moiety of a duplex system. Note the downward displacement and lateral position of the collecting system, the 'drooping lily' appearance.

Table 6.2 Renal length in children using ultrasound

Age	Mean renal length (cm)	SD
0–1 week	4.48	0.31
1 week to 4 months	5.28	0.66
4–8 months	6.15	0.67
8 months to 1 year	6.23	0.63
1–2 years	6.65	0.54
2–3 years	7.36	0.54
3–4 years	7.36	0.64
4–5 years	7.87	0.50
5–6 years	8.09	0.54
6–7 years	7.83	0.72
7–8 years	8.33	0.51
8–9 years	8.90	0.88
9–10 years	9.20	0.90
10–11 years	9.17	0.82
11–12 years	9.60	0.64
12–13 years	10.42	0.87
13–14 years	9.79	0.75
14–15 years	10.05	0.62
15–16 years	10.93	0.76
16–17 years	10.04	0.86
17–18 years	10.53	0.29
18–19 years	10.81	1.13

Reproduced with permission from Rosenbaum DM, Korngold E, Teel RL. Sonographic assessment of renal length in normal children. Am J Roentgenol 142:467–9, 1984.

parenchyma should be assessed for masses, cysts, calcifications, and echogenicity. Loss of corticomedullary differentiation, also referred to as medical renal diseases (MRD), can be seen in varied disorders, such as acute tubular necrosis, infections, glomerulosclerosis, or autosomal recessive polycystic kidney disease (ARPKD).

Evaluation of renal vessels

Utilizing duplex, color, and power Doppler imaging, renal ultrasound can characterize renal vascular flow. The renal arteries and veins, as well as smaller arcuate vessels, can be assessed for renal artery stenosis, renal vein thrombosis, or renal transplant rejection.

Fetal urogenital ultrasonography

Congenital anomalies of urogenital tract are found in 3–4% of the population.[2] Lethal urinary tract anomalies account for 10% of spontaneous pregnancy terminations.[3] A systematic prenatal sonographic approach includes evaluation of the amniotic fluid volume, characterization of genitourinary anomalies, and search for associated abnormalities such as VACTER (Vertebral, Anal atresia, Tracheoesophageal fistula, Radial and Cardiac). Normal fetal kidney has a lobulated appearance, with distinct pyramidal structures and variable corticomedullary differentiation (Figure 6.13).

Amniotic fluid

Prior to the 16th gestational week, amniotic fluid volume is partially independent of urine production, but a lack of fetal urine output after 16 weeks results in a rapid decline in amniotic fluid volume. Under these circumstances, the fetus develops classic 'Potters sequence', which includes low-set ears, beaked nose, clubfeet and hands, as well as growth retardation. Pulmonary hypoplasia is also a common secondary organ failure and is often the cause of significant morbidity and death in these patients. Lethal genitourinary anomalies are associated with minimal or no urine production, and include renal agenesis, bilateral multicystic dysplastic kidneys, infantile ARPKD, and severe posterior urethral valves.

Antenatal hydronephrosis

Antenatal dilatation of the renal collecting system is a common finding in the fetus. Dilatation of the collecting system is graded as pyelectasis or pelvic dilatation (Figure 6.14), caliectasis or calyceal dilatation (Figure 6.15), and hydroureter. It is important to note that sonography is unable to differentiate between a dilated urinary collecting system due to urinary obstruction and a non-obstructed dilated system due to abnormal ureteric muscle development, or vesicoureteral reflux.

Measurement of the anterior–posterior renal pelvic diameter (RPD) is commonly used to assess fetal hydronephrosis. In the

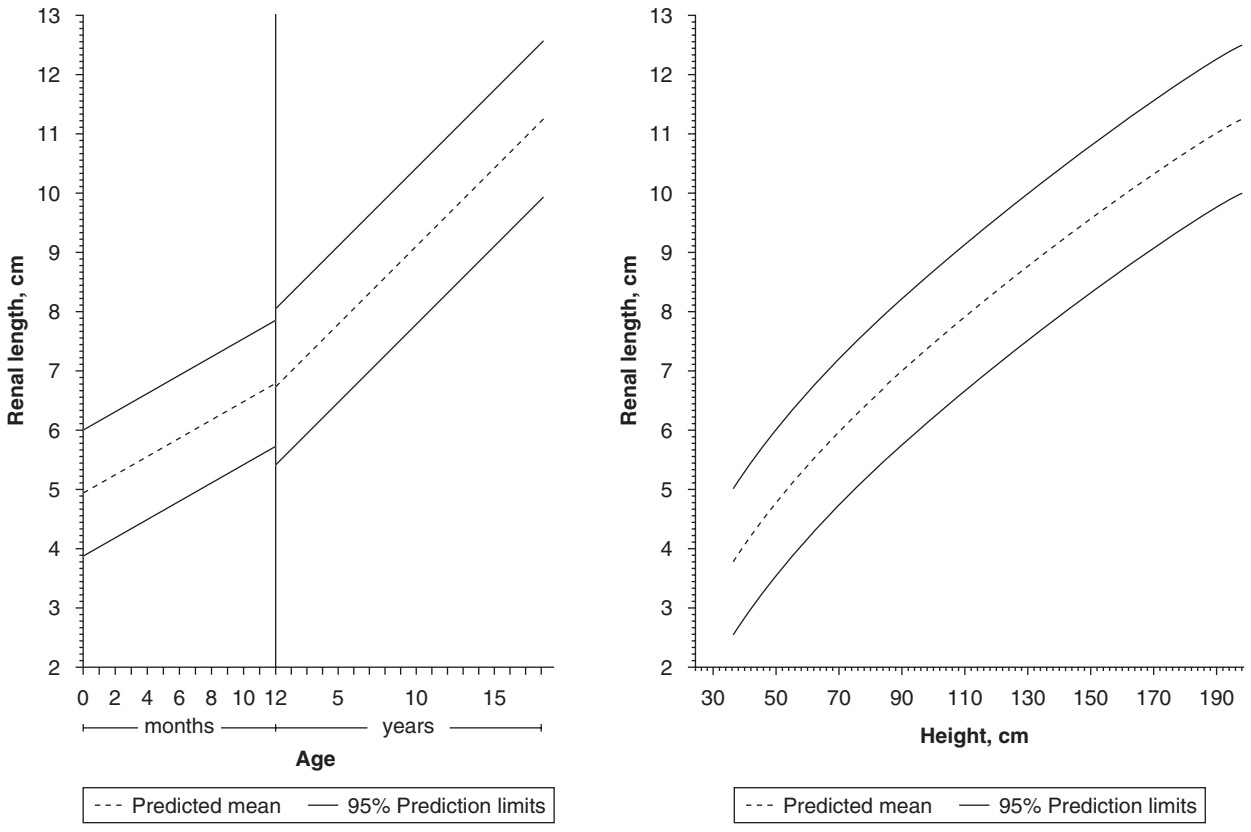

Figure 6.12 Renal size in children as determined by sonography. Age is represented in years unless otherwise specified. (Reproduced with permission from Am J Radiol Han BK, Babcock DS. Sonographic measurements and apperance of normal kidneys in children. Am J Roentgenol 145(3) 611–16.)

Table 6.3 Causes of abnormal renal size

Small kidney(s)
- Renal hypoplasia and dysplasia
- Renal arterial stenosis
- Reflux nephropathy
- Chronic kidney disease

Unilateral nephromegaly
- Acute pyelonephritis
- Renal vein thrombosis
- Renal tumor
- Hematoma
- Renal abscess
- Urinary tract obstruction, hydronephrosis
- Beckwith–Weidemann syndrome

Bilateral nephromegaly
- Polycystic kidney disease
- Acute glomerulonephritis
- Bladder outlet obstruction, hydronephrosis
- Bilateral Wilms' tumor
- Glycogen storage diseases
- Acute lymphatic leukemia (leukemic infiltrates)
- Lymphomas

second trimester, cut off for abnormal RPD is 4–6 mm, whereas in the third trimester cut off for abnormal ranges from 7–10 mm. Factors such as maternal hydration and size of the fetal bladder can affect the RPD measurement.[4] Calyceal or ureteral dilatation should always be regarded as an abnormal sonographic finding in a fetus, regardless of the renal pelvic size.[5]

Fetuses with mild hydronephrosis (RPD 4–7 mm at 18–23 weeks gestation) typically resolve prenatally (80%). Fetuses with moderate to severe pyelectasis (RPD > 7 mm or presence of caliectasis at 18–23 weeks) typically do not resolve prenatally, but up to 44% have been reported to resolve postnatally without any surgical intervention.[4]

When a fetus is diagnosed with unilateral or bilateral hydronephrosis, it is important to estimate its severity by the degree of dilatation. Also, a note is made of the state of the renal parenchyma, and whether the calyces and ureters are dilated. If both kidneys are affected, and the parenchyma is thinned or cortical cysts are noted, close prenatal follow-up is necessary due to the risk of oligohydramnios and progressive renal failure in the fetus.

Most infants identified prenatally with hydronephrosis are asymptomatic at birth. Treatment and postnatal imaging protocols continue to evolve. The infant should be placed on

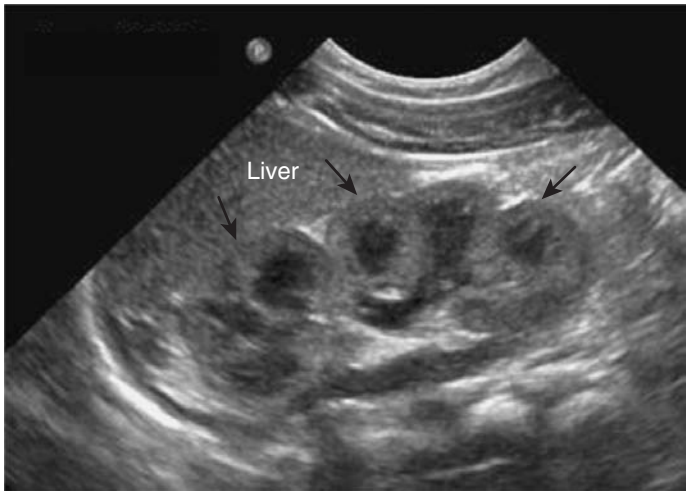

Figure 6.13 Renal ultrasound in a normal term infant. Fetal lobulations (arrows) are seen on the surface of the kidney. The renal cortex is more echogenic than the liver and the prominent renal pyramids are hypoechoic.

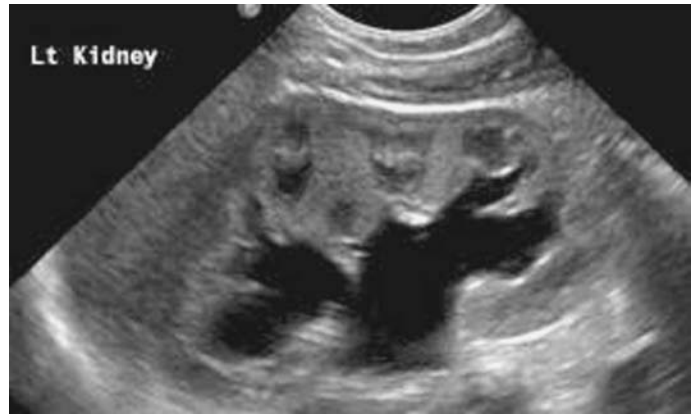

Figure 6.15 Renal ultrasound in an infant showing moderate pyelectasis and caliectasis. Cystogram and diuretic renal scan were normal, suggesting non-obstructive hydronephrosis.

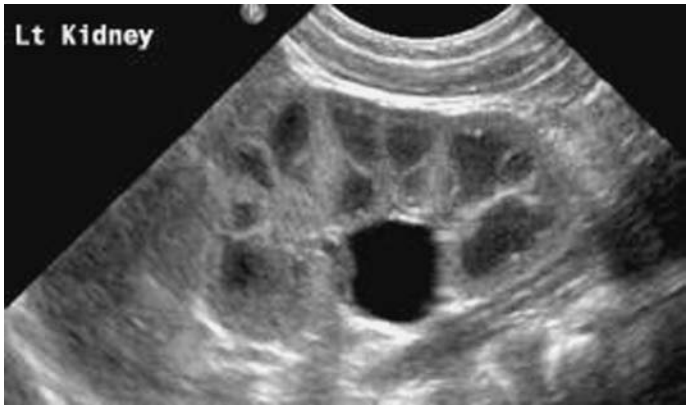

Figure 6.14 Renal ultrasound showing longitudinal image of the left kidney with mild dilatation of the renal pelvis.

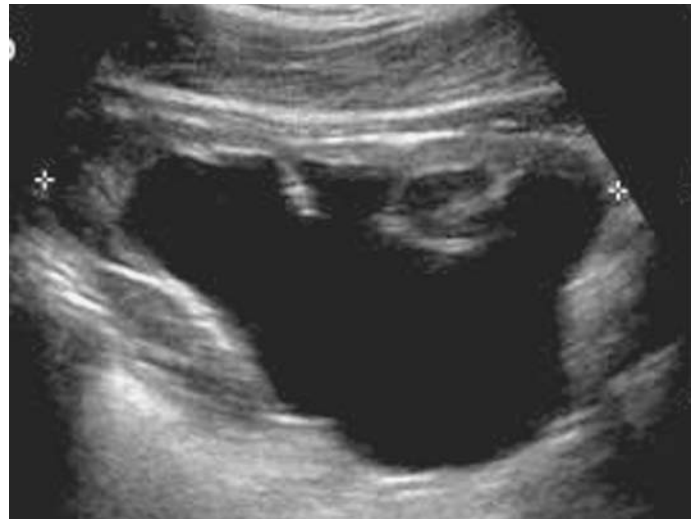

Figure 6.16 Renal ultrasound showing longitudinal view of the left kidney. Significant pelvic and calyceal dilatation and cortical thinning resulting from ureteropelvic junction obstruction is seen.

prophylactic antibiotics until the work-up is completed, if there is a concern that obstruction or VUR is present. Sonography should be avoided on the first day of life, since the neonate may be in a state of dehydration, which can underestimate the degree of hydronephrosis and result in a falsely negative ultrasound study.[5,6]

Sonographic evaluation soon after birth should be considered in all patients with bilateral severe fetal hydronephrosis, so that any required intervention can be provided. Because ultrasound does not screen for VUR, cystography should be considered in cases of hydronephrosis without any evidence of urinary obstruction. Need for a cystogram is less clear in cases where postnatal evaluation shows resolution of antenatal hydronephrosis. In the presence of a significant hydronephrosis and a normal cystogram, an isotope scan with furosemide is useful for further evaluation of the severity of obstruction.[7]

Obstructive uropathy

The most common anatomic level of obstruction within the urinary tract is at the level of the ureteropelvic junction (UPJ). Sonographically, the central pelvis and calyces are dilated with varying degrees of cortical thinning (Figure 6.16). The ureter is normal in size and usually not visualized. Obstruction at the ureterovesical junction is often due to a stricture, ureteroceles (Figure 6.17), or an ectopic ureteric insertion. Bilateral hydronephrosis can result from bladder outlet obstruction, such as posterior urethral valves. A thick trabeculated bladder wall

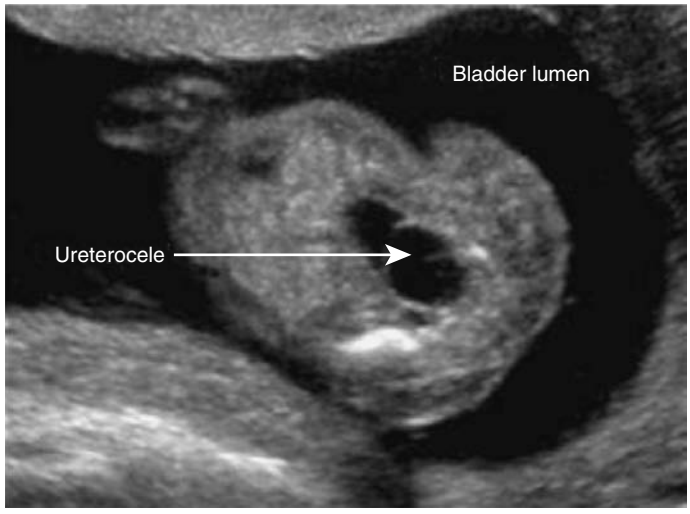

Figure 6.17 Prenatal ultrasound at 24 weeks gestation demonstrates a transverse image of bladder containing a cyst consistent with a ureterocele.

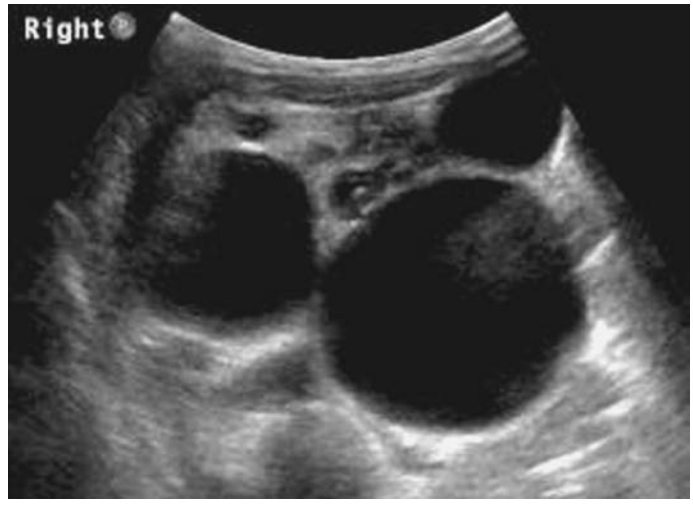

Figure 6.19 Transverse image of the right kidney in a patient with multicystic dysplastic kidney (MCDK) demonstrating multiple cysts of varying size that do not connect with each other. No normal renal parenchyma is present.

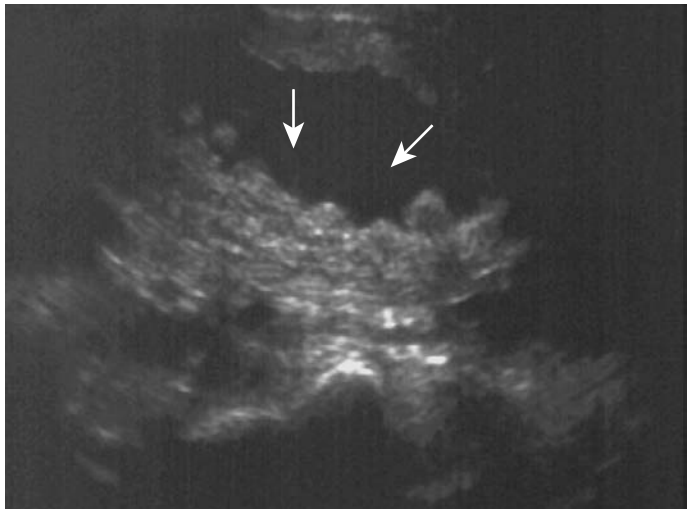

Figure 6.18 Ultrasound image of the urinary bladder showing thickened bladder wall and trabeculations of the mucosa (arrows) in a patient with neurogenic bladder.

noted on ultrasonography is suggestive of neurogenic bladder (Figure 6.18), and dilated posterior urethra may be indicative of posterior urethral valves.

Cystic diseases

A variety of inherited syndromes, genetic and chromosomal disorders, are associated with renal cystic disease.[8] Meckel–Gruber syndrome has cystic dysplastic kidneys, encephaloceles, and polydactyly. Trisomy 13 and 18 have cystic kidneys in 30% and 10%, respectively. Jeune's syndrome, short rib polydactyly, and Zellweger syndrome are autosomal recessive syndromes associated with cystic kidneys. Cysts of varying size and location can be found in autosomal dominant diseases such as tuberous sclerosis and von Hippel–Lindau disease. Tuberous sclerosis is associated with mental retardation, seizures, adenoma sebaceum, and ectodermal lesions. Approximately 40% of such patients have renal lesions that include cysts and angiomyolipomas. Angiomyolipomas are identified sonographically by their echogenic foci due to fat. Von Hippel–Lindau disease is associated with renal cysts and patients with the disease have an increased risk of renal cell carcinoma.

Multicystic dysplastic kidney (MCDK) is felt to be the result of failure of the ureteric bud to unite with or properly divide and stimulate the metanephric blastema. Sonographically, multiple non-communicating cysts of varying size are identified with minimal surrounding echogenic tissue (Figure 6.19). Unilateral MCDK is associated with contralateral renal anomalies in up to 25% of cases.[9] Complete urologic work-up is necessary in order to differentiate MCDK from severe UPJ obstruction in the affected kidney, and to exclude VUR in the contralateral kidney.[10]

Autosomal recessive polycystic kidney disease has a wide spectrum of clinical presentation, ranging from perinatal severe renal disease to the juvenile form with minimal renal disease, and dominant hepatic fibrosis. Kidneys are enlarged, echogenic as a result of microcysts, and corticomedullary differentiation is poor (Figure 6.20). Prenatal sonographic diagnosis of ARPKD can be made only in the second trimester. Kidneys may appear normal earlier in the gestation. The ARPKD locus has been mapped to proximal chromosome 6p, so families at risk can be evaluated with genetic testing in the first trimester.[11]

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the presence of cysts in the kidney and liver. Cysts may also be detected in the pancreas and spleen. Prenatally, the kidneys may appear normal, or large and echogenic with variable presence of cysts. Multiple cysts scattered throughout the parenchyma are the hallmark of ADPKD (Figure 6.21). Hemorrhage and calcifications can develop within larger cysts that appear heterogeneous sonographically.

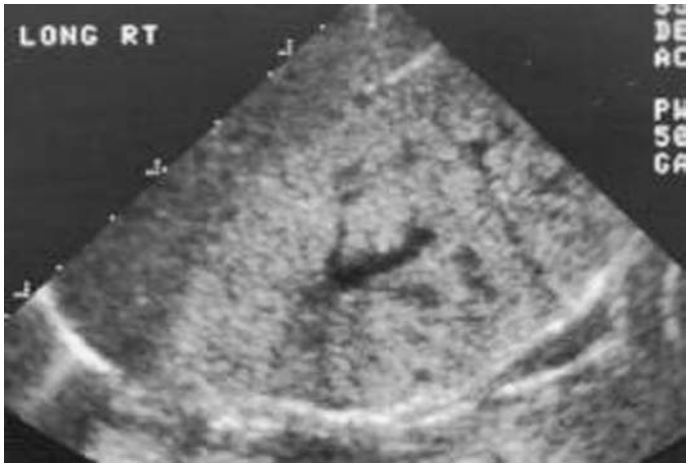

Figure 6.20 Renal ultrasound in an infant with autosomal recessive polycystic kidney disease (ARPKD). Longitudinal view of the kidney demonstrates an echogenic kidney. No clear evidence of cysts is seen.

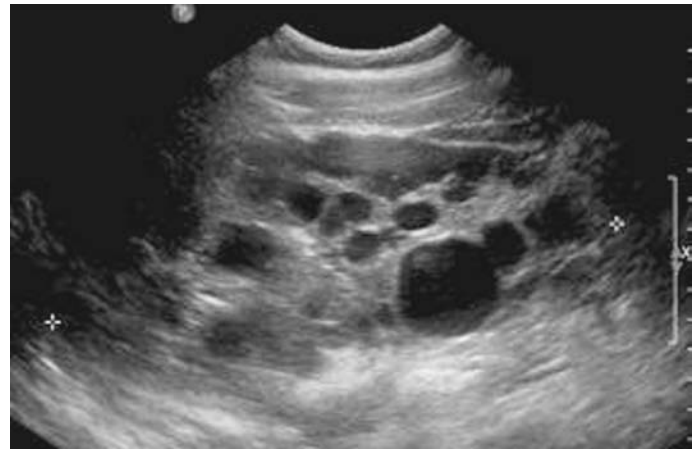

Figure 6.21 Renal ultrasound showing multiple cysts scattered throughout the renal parenchyma in a patient with autosomal dominant polycystic kidney disease (ADPKD).

Renal neoplasms

Ultrasound may be the first study to detect a renal tumor. Congenital renal neoplasms are rare. The most common fetal or neonatal tumor is the mesoblastic nephroma, also known as fetal renal hamartoma. Prenatally, it may present as a solid unilateral vascular mass with a whorled appearance. This benign tumor cannot be differentiated from a Wilms' tumor radiographically, and nephrectomy is generally indicated.[12]

Wilms' tumor, also known as nephroblastoma, usually presents as a large mass distorting the collecting system and the renal capsule. By ultrasound, the mass is typically solid, hyperechoic, and homogeneous. The mass may obstruct the collecting system and the renal tissue may be severely compressed into a thin rim. Hemorrhage and necrosis may make the tumor heterogeneous in appearance, and cysts have been reported. A Doppler ultrasound study is particularly useful in assessing the spread of the tumor into the renal vein and the inferior vena cava.

Cystic nephroma is a rare lesion seen in children and is considered to be benign. It is composed of multiple cysts of varying size. This mass is difficult to distinguish from a cystic Wilms' tumor, since both may appear well circumscribed, with multiloculated cysts and septations.

Lymphomatous involvement of the kidney is noted as single or multiple relatively hypoechoic masses. These may appear as discrete lobulated masses, although diffuse infiltration can also occur.

Computed tomography and magnetic resonance imaging

Computed tomography and magnetic resonance imaging are well-established cross-sectional imaging methods used for diagnosis of renal and retroperitoneal disease in children. Both methods yield relatively high spatial resolution images of the kidneys and the surrounding retroperitoneal structures. Thin section data sets obtained with CT can be used to reconstruct coronal, sagittal, and oblique imaging planes. However, a higher radiation exposure dose is needed for very thin acquisitions. Three-dimensional surface renderings can also be obtained when large density differences allow separation of various tissues, e.g. the high-density renal collecting system or contrast-enhanced renal vessels. MRI has the advantage of acquiring sectional images directly in virtually any anatomic plane without any radiation exposure.

Radiation exposure in CT

In general, basic CT data acquisition is fast, and newer versions of multidetector scanners can cover the abdomen of a child in only a few seconds. This acquisition gives a single phase of vascular and renal contrast enhancement. Multiple phases require additional acquisitions, incurring an additional radiation exposure. Even with the best of radiation reduction techniques, exposures remain in the order of hundreds of millirads to a full rad for every data acquisition.

Contrast nephrotoxity in CT and MRI

The intravenous contrast agents used in CT can cause nephrotoxicity. This risk is enhanced in patients with compromised renal function, dehydration, diabetes, and compromised systemic perfusion, and in those patients already on other nephrotoxic drugs.[13,14]

Ionic, high osmolality contrast agents have osmolality in the range of 1400–2070 mOsm/kg water, whereas 'low' osmolality, non-ionic agents range from 700 to 800 mOsm/kg water. Current recommendations for contrast administration include the use of

low osmolality and iso-osmolar agents, adequate hydration, and administration of the lowest possible contrast dose necessary for an adequate examination. *N*-acetyl cysteine, an antioxidant, may be used to ameliorate the nephrotoxic effects of the contrast drugs.[15]

MRI contrast agents have no demonstrable nephrotoxicity when given in doses that are typical of clinical use.[16] Gadolinium has been utilized successfully in adults with renal insufficiency.[17] The risk of serious adverse or allergic reactions is also lower than that of radiographic agents. For these reasons, MRI studies may be the preferred alternative to contrast-enhanced CT when renal function is compromised. It is important to note that no large-scale studies have analyzed the risk of rapid intravenous gadolinium contrast agent injections at the higher doses that are typically employed for MR angiographic studies in children.

Limitations of MRI

The dominant limitation of MRI arises from the longer overall imaging time required for a complete study. The procedure usually requires sedation for a minimum of 30–45 minutes in infants and young children. In addition, longer imaging times introduce a significant artifactual element engendered by physiologic motion from respiration, from gastrointestinal peristalsis, and even from cardiovascular pulsations.

Assessing renal function with CT and MRI

Whereas nuclear medicine studies have forged the early path to clinical application of imaging for determination of renal function, dynamic studies of renal perfusion and function have also been performed using MRI and CT.[18,19] CT use is limited because of a high radiation exposure required for serial sampling of the kidneys during passage of contrast through the kidneys. In MRI, serial sampling of signal intensity of kidneys can yield time–signal intensity curves of the transit of the contrast from which the glomerular filtration rate (GFR) can be calculated.[20] Gadolinium DTPA (gadolinium complexed with diethylenetriamine pentaacetic acid), which is filtered by glomeruli, is neither reabsorbed nor secreted by the renal tubules, is used as an imaging marker for studying renal perfusion, and GFR.

CT and MRI angiography

Rapid thin-section imaging, improved data reconstruction techniques, and rapid contrast injections have made it possible to create angiographic images from cross-sectional data sets. This obviates the need for invasive catheter angiography in children, and allows relatively low-risk performance of CT and MR angiograms. The spatial resolution and temporal resolution of these methods does not, however, approach that of traditional catheter angiography. However, demonstration of the aorta and central, first-, and second-order branch vessels can be achieved.

CT angiography involves a rapid intravenous injection of radiographic contrast material, combined with a rapid spiral volume acquisition. This is typically done in sedated, free-breathing infants and young children. Older children and adolescents can be coached to breath-hold, producing more accurate data with less bulk motion artifact. Three-dimensional images of the vessels are created from the acquired data. Limitations to the anatomic accuracy include uncompensated bulk motion, intrinsic pulsatile vascular motion, and some intrinsic CT artifacts.

MR angiography is a highly developed technique in adult imaging, and is used for evaluation of intrinsic aortic disease and evaluation of patients with possible renovascular hypertension.[21] With a rapid intravenous injection of gadolinium as the contrast agent, three-dimensional images of the central arterial and venous structures can be achieved (Figures 6.22 and 6.23). The small size of the vessels of small children make them more difficult to image than adults; nonetheless, parenchymal perfusion defects can be well demonstrated in smaller lobar and segmental vascular territories.

CT and MRI urography

The urine-filled collecting system can also be imaged for combined anatomic and physiologic information in dilated/obstructed and dilated/non-obstructed systems by performing MRI urography.[22,23] Following injection of gadolinium and its excretion into the urinary tract, T1-weighted images show strong signals from the collecting structures, whereas most other tissues show moderate or low signal intensity (Figure 6.24).

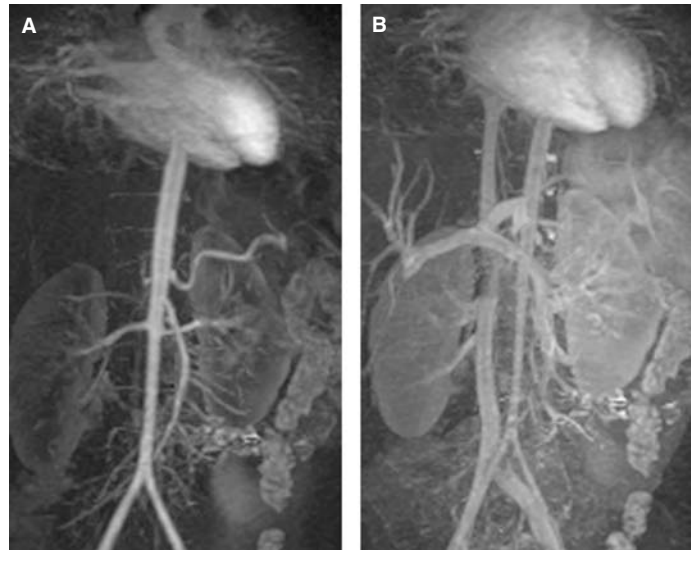

Figure 6.22 MR angiogram. (A) An arterial-phase image in a 4-year-old child showing the major central vascular structures of the abdominal arterial tree. (B) Filling of the venous structures and a general opacification of the parenchymal organs.

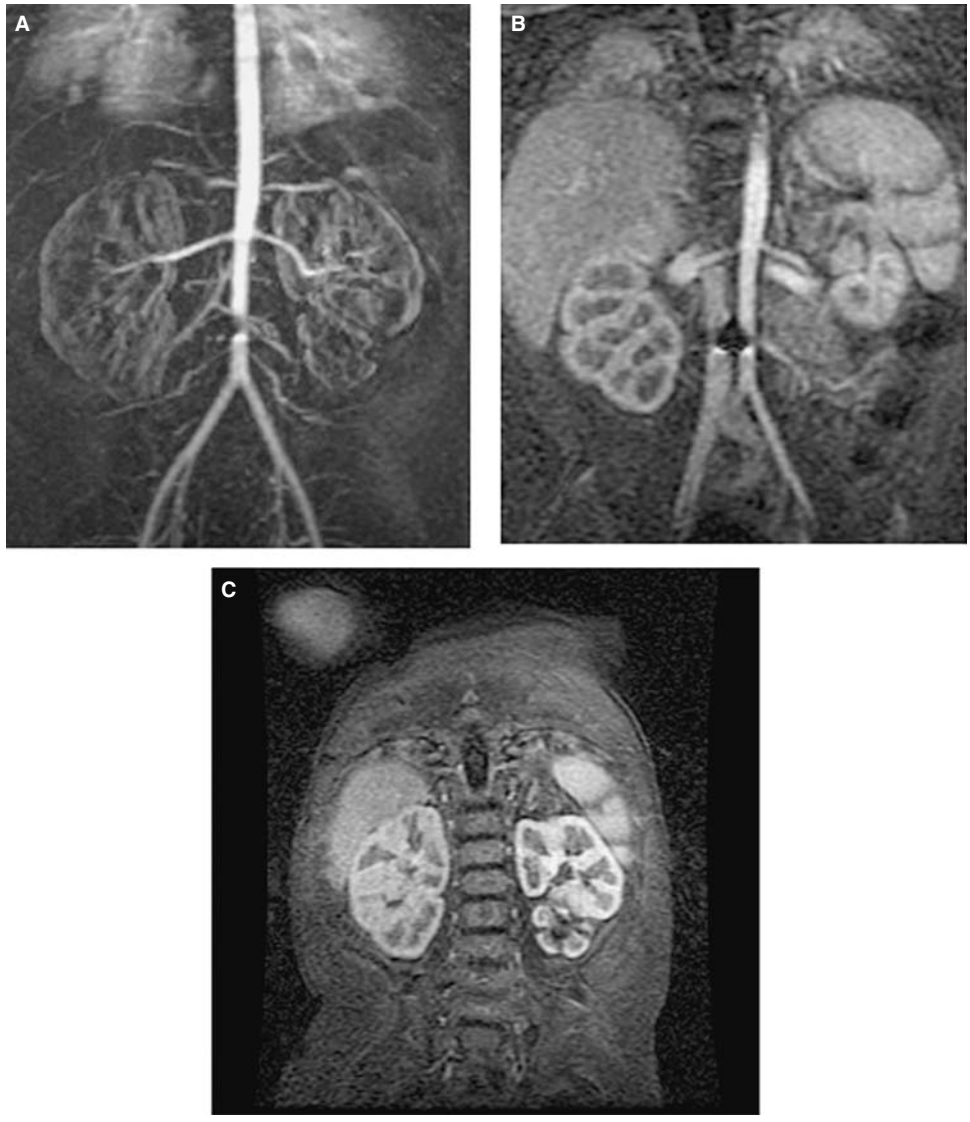

Figure 6.23 MR angiogram in a 4-month-old infant: (A) arterial, (B) venous/nephrographic, and (C) excretion phases.

Thus, the collecting systems can be imaged from the calyces up to the level of the urinary bladder. Differential uptake in the two kidneys, excretion, and clearance of the contrast can be demonstrated with rapid serial image sequences.

CT and MRI imaging in renal infections

CT and MRI are infrequently used modalities in the diagnosis of urinary tract infections. They can both be used as sensitive methods for detecting acute pyelonephritis as well as renal scarring. Ischemic focal defects in the renal parenchyma associated with acute pyelonephritis can be demonstrated with contrast-enhanced CT (Figure 6.25), as well as with contrast-enhanced MRI (Figure 6.26). A wedge-shaped parenchymal defect in renal cortex representing ischemic parenchyma can be seen in acute pyelonephritis. MRI has been shown to have diagnostic accuracy similar to cortical scintigraphy in a controlled blinded study in experimental animals.[24] The clinical utility of contrast-enhanced MRI studies has been documented in children with urinary tract infections.[25] Severe acute pyelonephritis may occasionally give rise to swelling and a sizeable mass lesion in the kidney, or 'lobar nephronia', which may mimic a neoplasm. The mass can be seen as arising from the renal cortex with variable contrast-enhancement patterns. Renal scars may also be detected with CT or MRI (Figure 6.27).

Renal abscess is recognized by CT as a poorly enhancing renal mass with a necrotic center. Diffuse bacterial or fungal microabscesses, or miliary renal infection, may be difficult to diagnose with CT or MRI. The kidneys may be enlarged but show a poor degree of enhancement. Discrete parenchymal lesions may not be evident on CT or MRI, especially in the early stage.

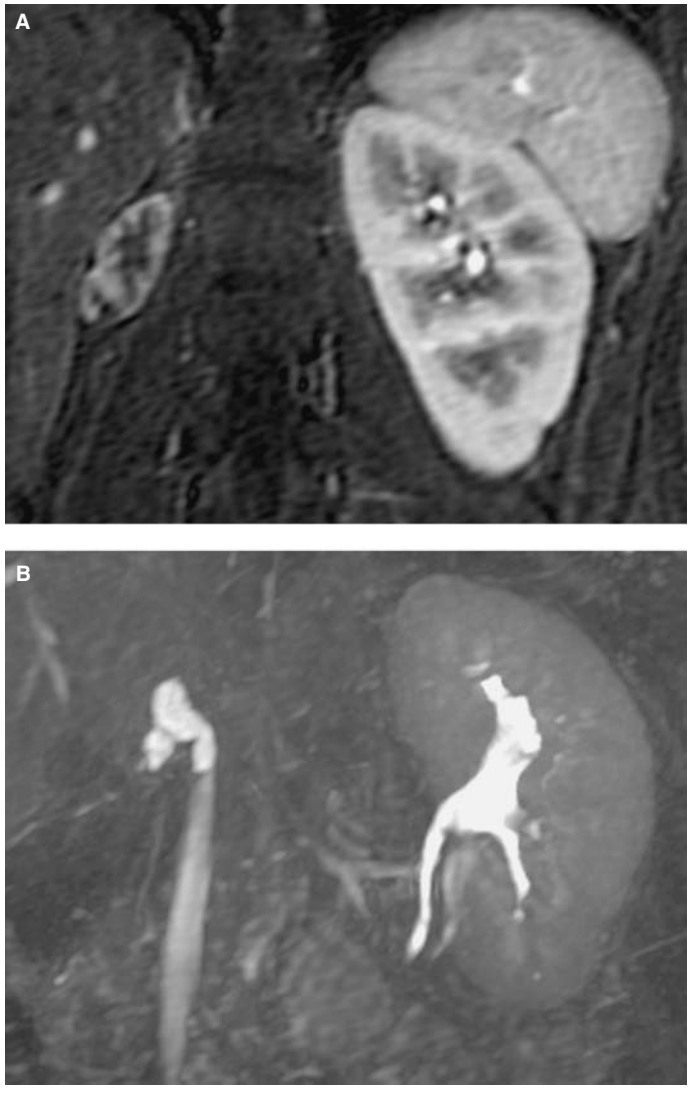

Figure 6.24 MRI, nephrogram, and urographic phases. (A) The early nephrogram is visible in this patient with right reflux nephropathy and contralateral renal hypertrophy. (B) The calyces, pelvis, and proximal ureters are well seen on the urographic phase as the gadolinium contrast agent is concentrated in the collecting system, and as the nephrogram fades.

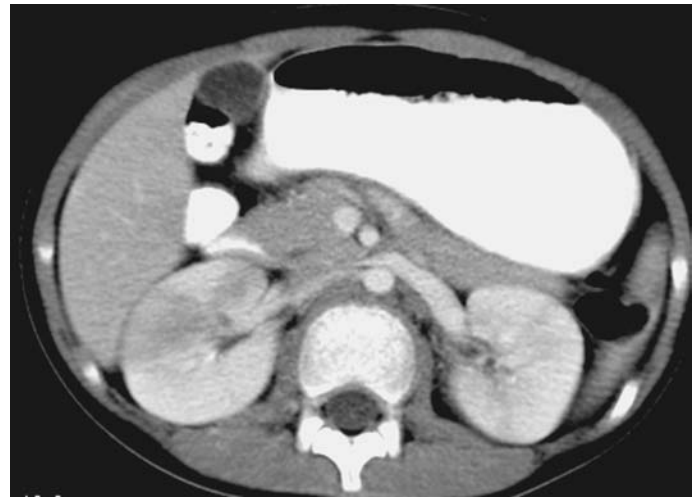

Figure 6.25 Contrast-enhanced CT in a patient with acute pyelonephritis showing the characteristic wedge-shaped defects in the right kidney. In addition, subtle defects are present in the left kidney.

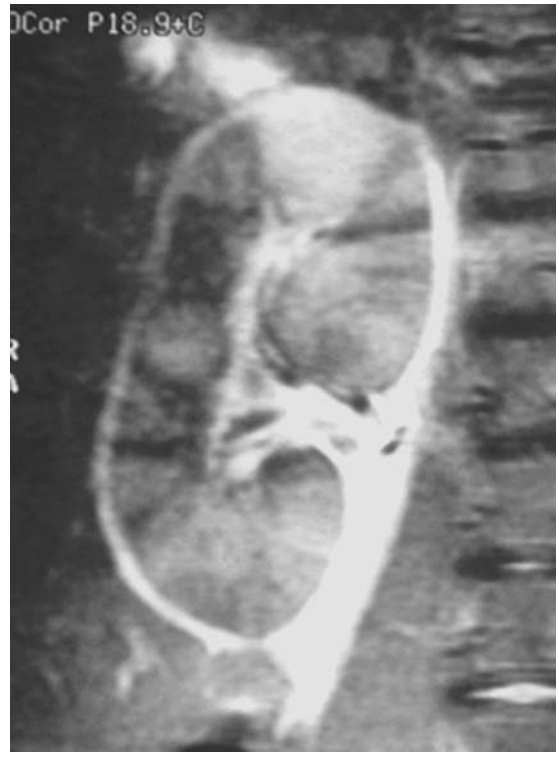

Figure 6.26 Gadolinium-enhanced inversion recovery MRI showing numerous wedge-shaped zones of abnormal high signal intensity throughout the right kidney. The abnormal perirenal, peripelvic, and periureteric high signal indicates perirenal inflammation.

Diagnosis of mass lesions by CT and MRI

Most patients with a known, palpable, or suspected abdominal mass lesion undergo CT or MRI cross-sectional imaging following preliminary anatomic 'triage' provided by ultrasonography. This serves to separate hydronephrosis and recognizable cystic lesions from solid, mixed cystic and solid, and lesions arising from perirenal tissues.

Tumors

Both CT and MRI provide a global anatomic view of the entire abdomen, as well as delineation of bowel, vascular structures, and normal renal parenchyma as distinct from pathologic renal tissue. Demonstration of bilateral renal masses or the presence of one dominant lesion with additional foci of parenchymal nodules suggests the presence of rests of metanephric blastema, or nephroblastomatosis (Figure 6.28). These are important diagnostic clues for early detection and risk assessment for Wilms' tumor, since nephrogenic rests are considered to be precursors of Wilms' tumor.[26–28]

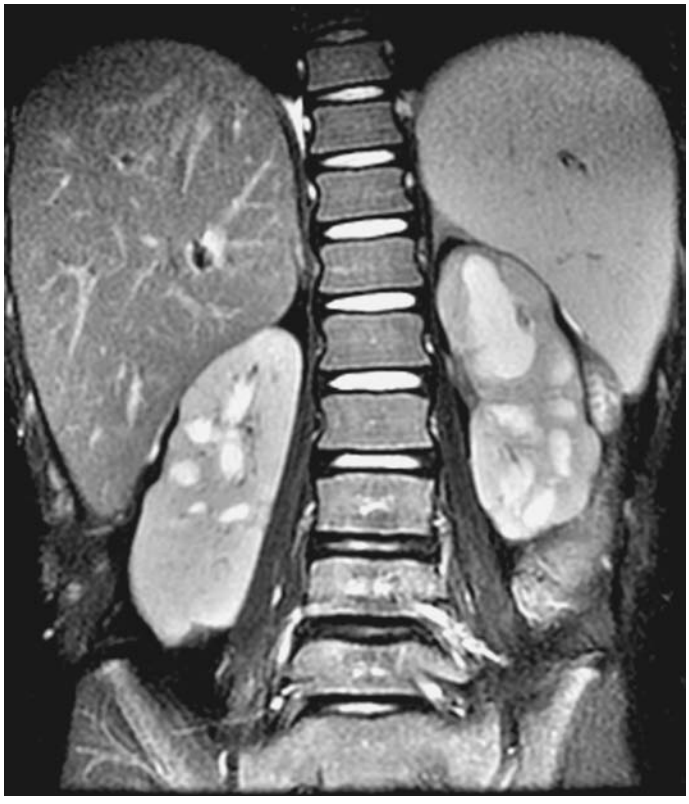

Figure 6.27 MRI coronal T2-weighted images showing irregularly dilated and clubbed calyces adjacent to focal zones of thinned renal parenchyma in a patient with inflammatory renal scarring.

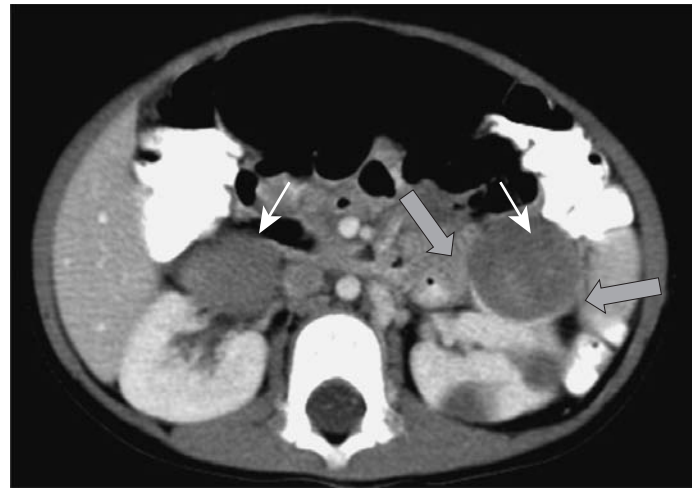

Figure 6.28 Wilms' tumor and nephroblastomatosis. CT shows multiple renal masses. One exophytic lesion is present in each kidney and represents nephroblastomatosis (white arrows). Grey arrows define the rim of renal tissue around the mass.

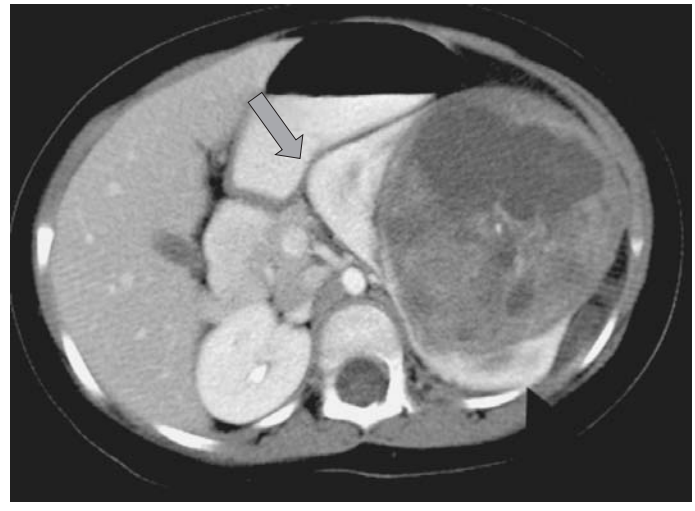

Figure 6.29 Contrast-enhanced CT scan in a patient with Wilms' tumor showing a necrotic but well–circumscribed mass arising from the left abdomen. The mass expands the normal renal tissue, creating a 'claw' appearance at the boundary between the mass and the normal renal tissue (grey arrow).

The CT and MRI provide important information about Wilms' tumor and its extension into the surrounding tissues. CT also provides a 'one-stop' investigation of the thoracic and abdominal cavities for detection of metastases. CT and MRI in Wilms' tumor usually demonstrate a renal mass that often compresses the surrounding tissue. Bilateral lesions may be present, and areas of hemorrhage or cyst formation may be seen within the tumor (Figure 6.29).

Renal cysts

CT and MRI play an important role in the evaluation of cystic masses of the kidney.[29,30] The dominant imaging features of a benign or simple cyst is its smooth, thin, and discrete outline. There are usually no internal debris, septations, or mural nodularity within the cyst. On CT or MRI studies, there is a homogeneous internal fluid character. Simple cyst fluid has a CT attenuation of less than 20 Hounsfield units on non-contrast images. Mural enhancement following intravenous injection of contrast agents is either minimal or completely absent. Very slight enhancement may represent compressed normal renal parenchyma around the wall of the cyst, or may result from imaging artifacts such as partial volume effect within adjacent tissue. Following any acute hemorrhage, simple cysts may develop a single thin internal septation and may have some internal debris following. Acute hemorrhage may be seen as a high attenuation value on CT (Figure 6.30 A,B) or as typical hemoglobin degradation products on MRI.

Some cystic masses may communicate with the renal collecting system. These are diagnosed when contrast agents opacify the cyst on delayed images, indicating a calyceal diverticulum or a pyelogenic cyst (which communicates directly via the renal pelvis). A non-enhancing cystic mass at the renal pelvis indicates a parapelvic cyst, which is an encysted lymphatic collection that often follows trauma or surgery.

In ARPKD, the methods of CT and MRI also play a largely supportive imaging role following ultrasonography. The characteristic pattern consists of diffusely enlarged kidneys with uniformly high signal intensity on T2-weighted images.[31]

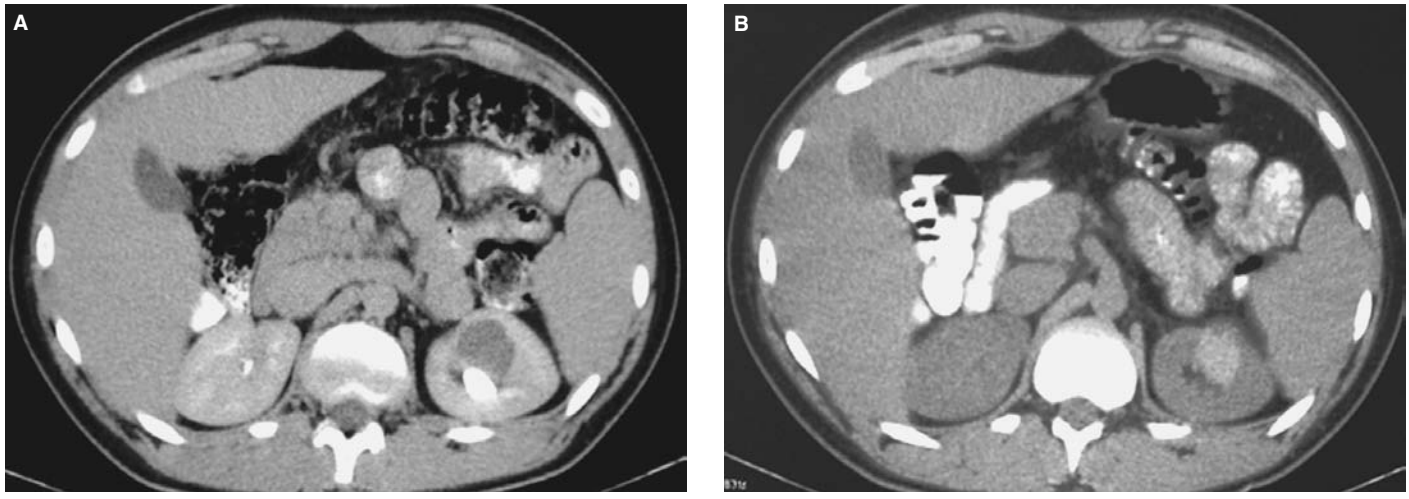

Figure 6.30 (A) Axial CT shows a well-defined fluid-containing cyst in the left kidney. (B) Following an episode of acute flank pain, CT reveals a generalized increased attenuation value of the mass, suggestive of acute hemorrhage.

In ARPKD, CT and MRI provide a more global anatomic view of the associated liver disease and its complications. Biliary disease can also be demonstrated by CT and MRI studies.

Multiple renal cysts may be the primary renal manifestation of important heritable multi-organ disorders such as ADPKD, tuberous sclerosis, Von Hippel–Lindau disease, Jeune's syndrome, and Zellweger syndrome.[32] Whereas ultrasound may demonstrate only a few lesions in early ADPKD, CT and MRI may be more helpful in demonstrating the diagnostic renal lesions.[27] In addition, CT and MRI allow visualization of pancreatic, splenic, or hepatic cysts associated with ADPKD.

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7 Radionuclide imaging

Eglal Shalaby-Rana, Mary Andrich, and Massoud Majd

The chief advantage of radionuclide imaging in pediatric nephrourology over other imaging modalities is its ability to provide quantitative functional data. These imaging techniques include renal scintigraphy, radionuclide cystography, and pheochromocytoma imaging. Pharmacologic interventions, such as the administration of furosemide or captopril in association with renal imaging, can further improve diagnostic accuracy. Additionally, overlying gas, stool, or plastic tubing does not hamper acquisition of imaging data. In some radionuclide imaging procedures, the ionizing radiation exposure is significantly less than with other similar radiographic procedures.

Renal scintigraphy

Radiopharmaceuticals

Several different ^{99m}Tc-labeled radiopharmaceuticals are currently available for imaging of the kidneys. The clinical indication determines which of the following radiopharmaceuticals is used.

1. ^{99m}Tc-Mercaptoacetyltriglycine (MAG3)
^{99m}Tc-MAG3 is primarily cleared by tubular secretion, allowing excellent visualization of the collecting systems, ureters, and bladder. Evaluation of the renal parenchyma may also be adequately performed with this agent.

2. ^{99m}Tc-Diethylenetriamine pentaacetic acid (DTPA)
^{99m}Tc-DTPA is primarily filtered by the glomeruli, allowing visualization of the collecting systems, ureters, and bladder. ^{99m}Tc-DTPA is the agent of choice for determination of glomerular filtration rate (GFR).

3. ^{99m}Tc-Dimercaptosuccinic acid (DMSA)
Approximately 40% of ^{99m}Tc-DMSA is filtered by glomerular filtration and excreted in urine, while 60% is fixated in the cortical tubular cells. Selective tubular handling and absence of interference from pelvicalyceal activity makes ^{99m}Tc-DMSA an ideal imaging agent for the evaluation of renal parenchyma. Delayed imaging can define focal parenchymal abnormalities, such as those seen with acute pyelonephritis, renal scarring, infarcts, and masses.

4. ^{99m}Tc-Glucoheptonate (GHA)
^{99m}Tc-GHA is cleared primarily by glomerular filtration (80–90%), with 10–20% cortical tubular fixation. This allows for cortical imaging. However, the cortical fixation is about one-third that of ^{99m}Tc-DMSA, making this compound less desirable for renal cortical scans.

Imaging techniques

With radiotracers that are primarily filtered or secreted (DTPA, MAG3, and GHA), sequential dynamic posterior images of the kidneys are obtained immediately after injection of the radiotracer, for 20–30 minutes. This constitutes a conventional renal scan. With cortical radiotracers (DMSA, GHA), imaging is done 1.5–2 hours after injection. Planar imaging, using high-resolution parallel hole and pinhole collimators, and/or SPECT (single-photon emission computed tomography) may be carried out.

Differential renal function

Differential renal function can be calculated on renal scans with any of these renal agents. The calculation is based on the relative amount of radiopharmaceutical extracted by each kidney. Regions of interest are drawn around each kidney and the total number of counts are then added. The relative percentages of counts in the two kidneys are calculated, and used to determine differential renal function. This may also be performed for segmental regions in the kidney, such as upper and lower moieties of a duplex system. When using ^{99m}Tc-DTPA or ^{99m}Tc -MAG3, the differential renal function is estimated from the early images that precede entry of tracer into the collecting system, usually during the second minute after radionuclide injection. With the use of ^{99m}Tc-DMSA or ^{99m}Tc-GHA, the differential function is calculated on the cortical phase, 1.5–2 hours after radionuclide injection.

Glomerular filtration rate

The use of radionuclide techniques eliminates the need for urine collection and is the method of choice for determining an accurate GFR in infants and children. The radioactive tracers

used for the determination of GFR are carbon-14 (^{14}C) inulin, iodine-125 (^{125}I) iothalamate, chromium-51 (^{51}Cr) ethylenediaminetetraacetic acid (EDTA), and ^{99m}Tc-DTPA. ^{51}Cr EDTA is commonly used in Europe, but ^{99m}Tc-DTPA is the most widely used tracer in the United States. DTPA meets the criteria for an ideal GFR agent except for the fact that 5–10% of the injected dose becomes protein-bound.

Several radionuclide imaging techniques are available for calculating GFR.[1–3] The most commonly used method in children involves injection of a radiotracer, followed by drawing of 2–3 blood samples, 2–3 hours after injection. These blood samples are centrifuged to yield plasma, and radioactivity is counted in the samples, using a well counter. Calculation of GFR is based on plasma clearance of the tracer. Another method uses volume distribution to calculate GFR in children. This technique uses a single plasma sample taken 2 hours after the injection of a dose of ^{51}Cr-EDTA.[4]

Renal transplant evaluation

Radionuclide imaging using ^{99m}Tc-MAG3 or ^{99m}Tc-DTPA provides an accurate, non-invasive, and non-nephrotoxic technique for evaluation of renal blood flow and function of the transplanted kidney (Figure 7.1).[5]

Vascular obstruction

Absence of flow in the initial post-transplant scan indicates either vascular obstruction (arterial or venous) or hyperacute rejection. These entities cannot be distinguished on renal scan, although hyperacute rejection is almost non-existent now due to extensive preoperative testing of the recipient.

Acute tubular necrosis

Scintigraphically, the blood flow to the renal transplant is normal, but the function is diminished in acute tubular necrosis (ATN). This is manifested by progressive parenchymal tracer accumulation and delay in excretion, and in severe cases by lack of any tracer excretion over the 30-minute imaging sequence (Figure 7.2). Toxicity from calcineurin inhibitors, cyclosporine, and tacrolimus may also cause similar scintigraphic changes. The distinguishing feature is the time of onset, being much later (2–3 weeks postoperative) with calcineurin inhibitor nephrotoxicity, and during immediate post-transplant period in the case of ATN.

Allograft rejection

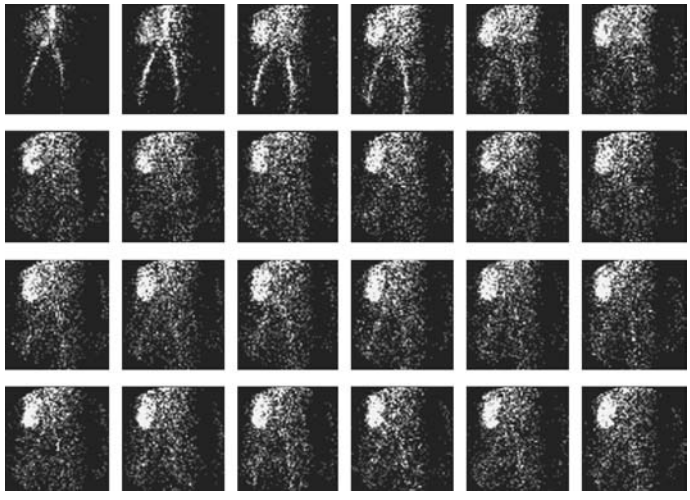
The scintigraphic findings of acute rejection are decreased perfusion and decreased function, in contrast to ATN, where renal perfusion is preserved. ATN and acute allograft rejection may coexist, and differentiation may be difficult. Chronic rejection occurs a few months to years after renal transplantation and evolves slowly. Serial renal scans demonstrate a gradual decrease in perfusion and function.

Perinephric fluid collection

Perinephric fluid collections leading to partial obstruction of the urinary tract or compression of the vascular pedicle can occur in renal transplants. On the early scintigraphic images (first 30 minutes), perinephric fluid collections appear as a photopenic defect surrounding the kidney or its vicinity. Delayed imaging usually shows accumulation of tracer in this photopenic area if the collection is a urinoma. In the case of hematoma or lymphocele, the area remains photopenic.

Captopril-enhanced renography

In the presence of renovascular hypertension (RVH), angiotensin II causes constriction of the efferent arterioles, and GFR may remain at or near normal level. Therefore, the conventional ^{99m}Tc-DTPA or ^{99m}Tc-MAG3 renal scan is often



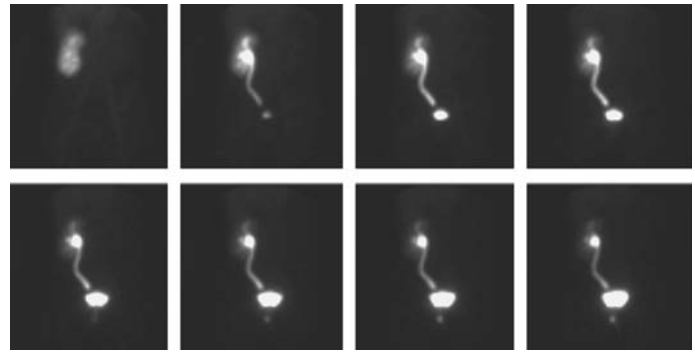


Figure 7.1 Renal transplant showing normal MAG3 renal scan. (A) Flow images (1-second images) show prompt flow to the kidney, within 2 frames of the aorta. (B) Dynamic functional images demonstrate good parenchymal extraction, excretion, and drainage.

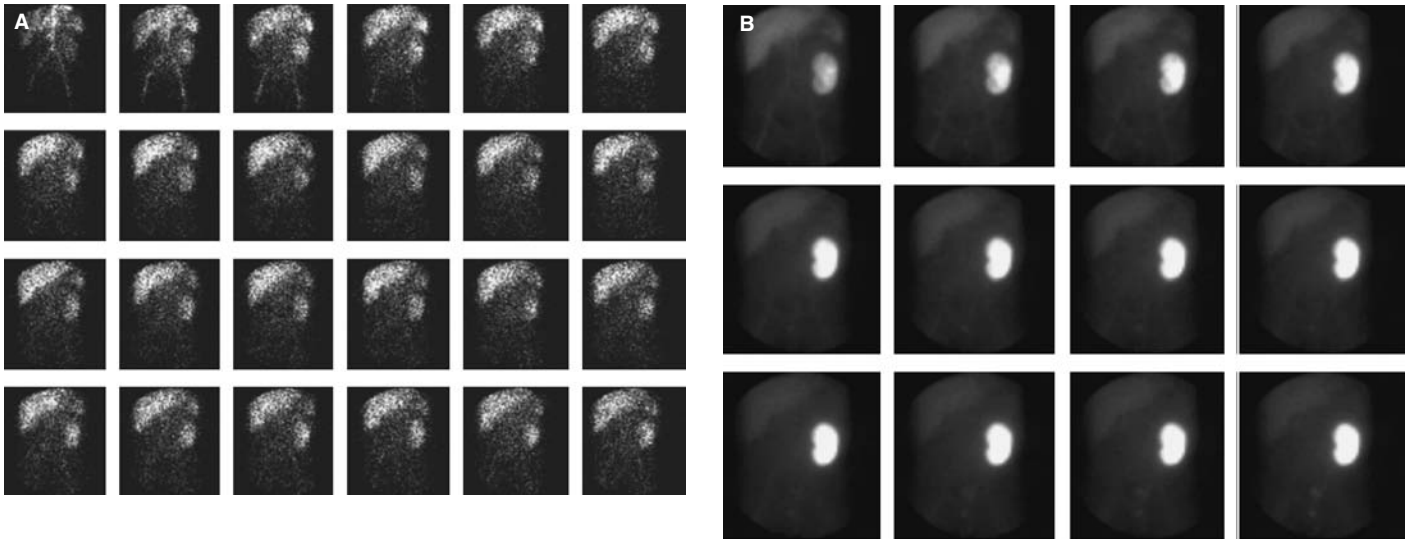


Figure 7.2 Renal transplant showing acute tubular necrosis (ATN) of a transplanted kidney. (A) Normal MAG3 flow images (1-second images). (B) MAG3 dynamic functional images showing good cortical uptake with almost no excretion of tracer by 30 minutes and significant cortical retention.

normal. Following administration of an angiotensin-converting enzyme inhibitor (ACEI) such as captopril, the efferent arterioles become dilated, which causes deterioration of renal function, detectable on the renal scan.

Technique

Although the original work in children was performed using ^{99m}Tc-DTPA,[6] ^{99m}Tc-MAG3 and ^{99m}Tc-DMSA have also been used for captopril enhanced renography.[7–9] For blockade of the renin–angiotensin system, either captopril (1 mg/kg, maximum dose 50 mg, given orally), or enalaprilat (0.03–0.04 mg/kg, given intravenously) may be used. Use of calcium channel blocking agents at the time of the study may cause false-positive/false-negative results. Therefore, these medications should be discontinued prior to the study.[10]

If the patient is not on ACEI therapy, a conventional baseline renal scan is obtained. A repeat renal scan is then obtained 1 hour after oral administration of captopril or 10 minutes after intravenous administration of enalaprilat. Renogram curves are generated for both the pre- and the post-ACEI scans (Figure 7.3A–D). A commonly used adaptation in adults is to do a post-ACEI scan first, and if normal, the examination is finished. If any abnormality is seen, the patient returns at a later time for a repeat scan without the ACEI.

Interpretation

The scintigraphic manifestation of decreased renal function after administration of ACEI depends on the radiotracer used. With ^{99m}Tc-DTPA, there is decreased extraction and delayed appearance of tracer in the collecting system. With ^{99m}Tc-MAG3, there is prolonged cortical retention of tracer. A positive study is strongly suggestive of renovascular hypertension and requires further investigation by arteriography (Figure 7.3E,F). A negative study after a single dose of ACEI does not necessarily exclude the diagnosis of RVH. In patients in whom there is a strong clinical suspicion, the scan may be repeated after the patient has been on ACEI for several days. Occasionally, the follow-up scan may become positive after 3–4 days of therapy.

Cortical imaging

Renal cortical scans are primarily used for the diagnosis of acute pyelonephritis and renal cortical scars. Other indications include search for an ectopic kidney, renal infarct, and evaluation after renal trauma. Renal cortical scintigraphy is obtained by high-resolution planar imaging or SPECT, 1.5–2 hours following the injection of ^{99m}Tc-DMSA or ^{99m}Tc-GHA.

Acute pyelonephritis

The diagnosis of acute pyelonephritis may not always be reliably made on the basis of standard clinical criteria alone.[11] Cortical scintigraphy has been shown to be a useful adjunct in the diagnosis of acute pyelonephritis,[12,13] and is comparable in accuracy to both CT and MRI.[14]

The scintigraphic features of acute pyelonephritis consist of decreased uptake without loss of cortical volume. There may be three different patterns: focal, multifocal, or diffuse (Figure 7.4B,C). Cortical defects are not specific for acute pyelonephritis and must be interpreted within the clinical context.

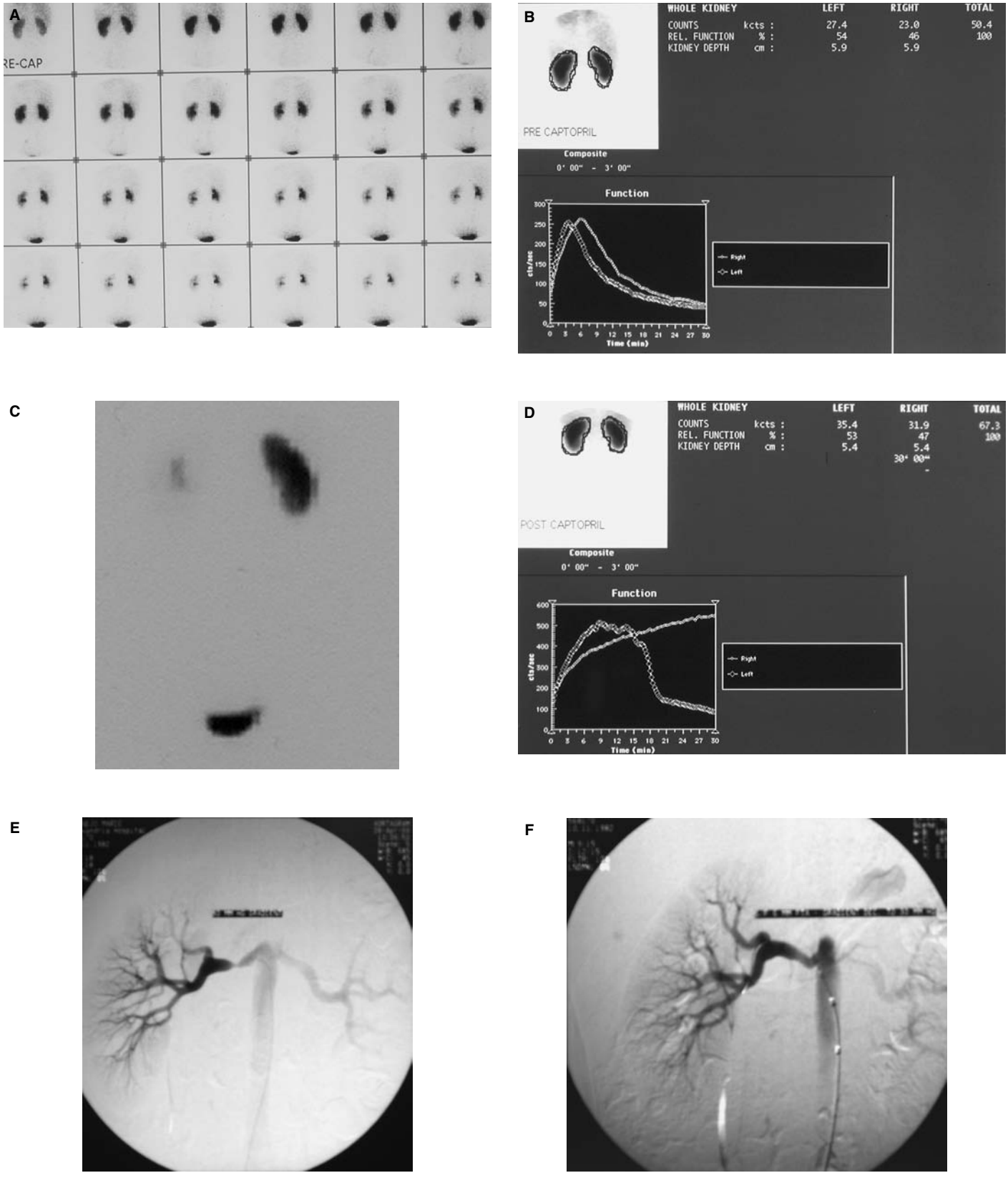


Figure 7.3 Right renal artery stenosis. (A) Pre-captopril MAG3 images showing normal renal scan. (B) Pre-captopril time–activity curve demonstrating normal and symmetric clearance from both kidneys. (C) Post-captopril MAG3 renal scan showing significant cortical retention on the right side and normal clearance on the left side. (D) Post-captopril curve showing rising time–activity curve on the right as compared to B. (E) Renal arteriogram demonstrating stenosis in right renal artery in this patient. (F) Post balloon angioplasty injection showing successful dilatation with now normal caliber of previously stenotic segment.

Renal scars

Photopenic defects associated with volume loss represent renal scars that are indicative of previous episodes of acute pyelonephritis (Figure 7.4D).[15,16] Patients with ^{99m}Tc-DMSA evidence of acute pyelonephritis should have a repeat renal scan 6–12 months later in order to assess long-term outcome of the infection. It has been shown that approximately 60% of all foci of acute pyelonephritis, in the absence of high-grade vesicoureteral reflux (VUR), resolve without scar formation.[17]

Ectopic kidney

The use of cortical scintigraphy is also helpful in the detection of ectopic kidney associated with ectopic ureteral insertion in girls who present with urinary incontinence.[17,18] Such an ectopic kidney is typically small, located in the pelvis, and may be difficult to locate by sonography due to overlying bowel loops. Although the function is usually poor, the ectopic kidney can be easily detected by anterior planar or SPECT cortical imaging.

Diuresis renography

Diuresis renography is utilized for determining the presence and level of obstruction within the urinary tract. It has been shown to be nearly as sensitive in detecting urinary tract obstruction as pressure perfusion studies, such as the Whitaker test.[19] Diuresis renography is indicated if significant hydronephrosis and/or hydroureter is present, and VUR has been excluded as the cause. Diuresis renography plays a vital role in the management of hydronephrosis/hydroureter in children, especially in neonates. Unlike hydronephrosis in the older child and adults, neonatal hydronephrosis is often dynamic, and may worsen or improve over time.[20] Therefore, serial imaging is often needed.

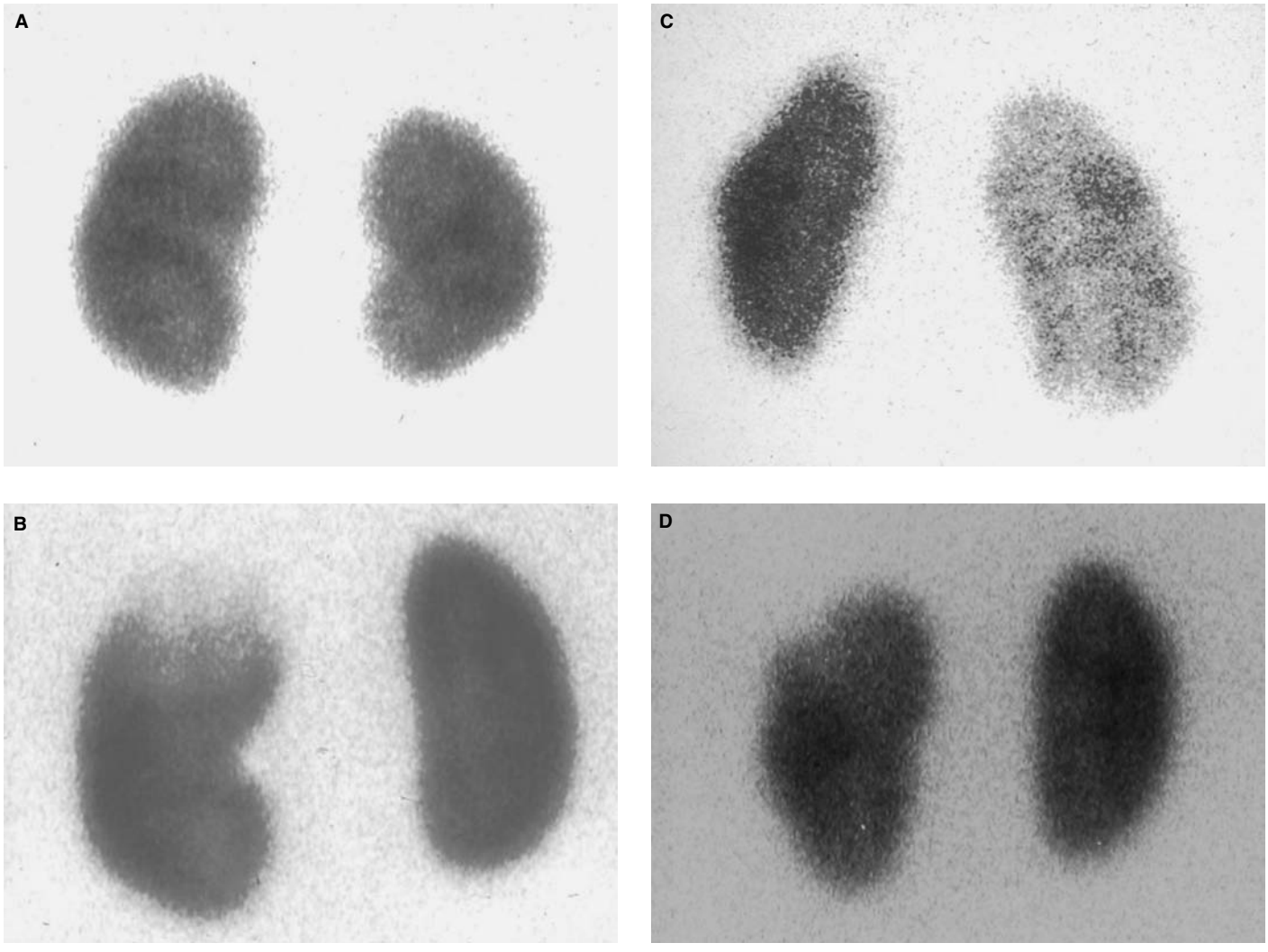


Figure 7.4 DMSA cortical renal scans. (A) Normal bilateral kidneys. (B) Focal acute pyelonephritis, upper pole left kidney. (C) Diffuse acute pyelonephritis, right kidney. (D) Focal scar, upper pole left kidney.

Technique

The technique used in our institution has been adopted and formulated into recommendations by the Society for Fetal Urology and the Pediatric Nuclear Medicine Council.[21] Institutional variations in the techniques may, however, exist. The parents are instructed to maintain the child's normal hydration status, and feedings are not withheld. An intravenous catheter is placed and intravenous hydration is begun. Placement of an indwelling bladder catheter is recommended in order to eliminate the effect of increased intravesical pressure on post-diuresis drainage. In addition, the catheter serves to alleviate patient discomfort, decrease the likelihood of VUR, and reduce gonadal radiation exposure from radioactive urine. ^{99m}Tc-MAG3 is then injected and a conventional renal scan is obtained. When the dilated system is completely filled with the tracer, furosemide (1mg/kg, maximum dose 40 mg) is injected intravenously and sequential dynamic renal images are obtained for 30 minutes. Furosemide can be injected simultaneously with MAG3, known as the 'F+0' method.[22]

Urine output is recorded during the 30 minutes after diuretic administration to assess adequacy of response by the kidneys. If significant residual tracer is noted in the dilated collecting system after the furosemide renogram, static renal images are obtained before and after the patient is held upright for 15 minutes to assess the effect of gravity on drainage.[23] After completion of imaging, time–activity curves are generated from the diuretic renogram and clearance half-times are generated by the computer. The half-time represents the time needed for half of the activity to clear from the collecting system after administration of diuretic.

Interpretation

Interpretation is made by examining the images in conjunction with the quantitative data, including half-times, post-upright clearance, and the shape of the curve (Figure 7.5). It may be difficult to establish the diagnosis of urinary obstruction based on the quantitative data obtained on a single renal scan, especially in the neonate. Rather, the initial renal scan often provides a baseline for follow-up renal scans and a trend in the quantitative data is used to establish the diagnosis of urinary tract obstruction.

Factors affecting the shape of the renogram curve and the rate of washout of tracer from the kidney include the degree of obstruction, renal function, capacity and compliance of the dilated system, state of hydration, bladder fullness, dose and timing of diuretic injection, and patient position.

Scintigraphy in pheochromocytoma

The localization of pheochromocytoma may be accomplished using ^{123}I-MIBG *m*-iodobenzylguanidine or ^{111}In octreotide scintigraphy. The detection of this tumor by ^{123}I-MIBG is based upon uptake by the pheochromocytoma cells of the MIBG, which is a pharmacologic analog of the false neurotransmitter guanethidine. The uptake, however, appears to be size-dependent. Improved diagnostic sensitivity is noted with tumors that are more than 1cm in size.[24] The sensitivity is even less with octreotide, a somatostatin receptor, but the complementary use of this radiotracer with ^{123}I-MIBG may be useful.[24] Recent data have shown positron emission tomography (PET) imaging utilizing ^{18}F DOPA to be extremely sensitive (100%) compared with ^{123}I-MIBG scanning (71%) in the diagnosis of primary pheochromocytoma.[25]

Radionuclide cystography

Whereas VUR is often diagnosed using fluoroscopic voiding cystourethrography (VCUG), radionuclide cystography (RNC) is an alternative method that can be used. Two types of RNC are used in clinical practice:

- the more commonly used direct (retrograde) RNC
- the indirect (intravenous) RNC.

Direct radionuclide cystography

The technique for direct RNC is similar to that of VCUG, except that radioisotope and saline are used instead of radiopaque contrast media. Imaging is begun immediately and continues through the end of voiding. Thus, intermittent or transient reflux is imaged. If reflux is seen, the volume at which reflux occurred is recorded (Figure 7.6). Direct RNC offers several advantages over VCUG. By far the greatest of these is the significantly low gonadal radiation dose, less than 5 mrads in girls and less than 2 mrads in boys.[26] Because of the continuous monitoring, RNC may be more sensitive than VCUG in the detection of reflux.[27] The major disadvantage of direct RNC, due to its limited spatial resolution, is its inability to evaluate the urethra and grade reflux accurately. Minor bladder wall abnormalities such as diverticula may also remain undetected.

Due to its relatively low radiation burden,[28] direct RNC is the imaging method of choice for follow-up in patients with known VUR, especially since these children undergo serial evaluations. Direct RNC is also an ideal screening tool in the evaluation of asymptomatic siblings (both girls and boys) of patients with known VUR. The prevalence of sibling reflux in an index case may be as high as 32%.[29] Finally, direct RNC is best suited in the initial work-up of VUR in girls, in whom urethral anomalies are rare. Direct RNC is not recommended for the initial evaluation in boys, because of its inability to evaluate the urethra.

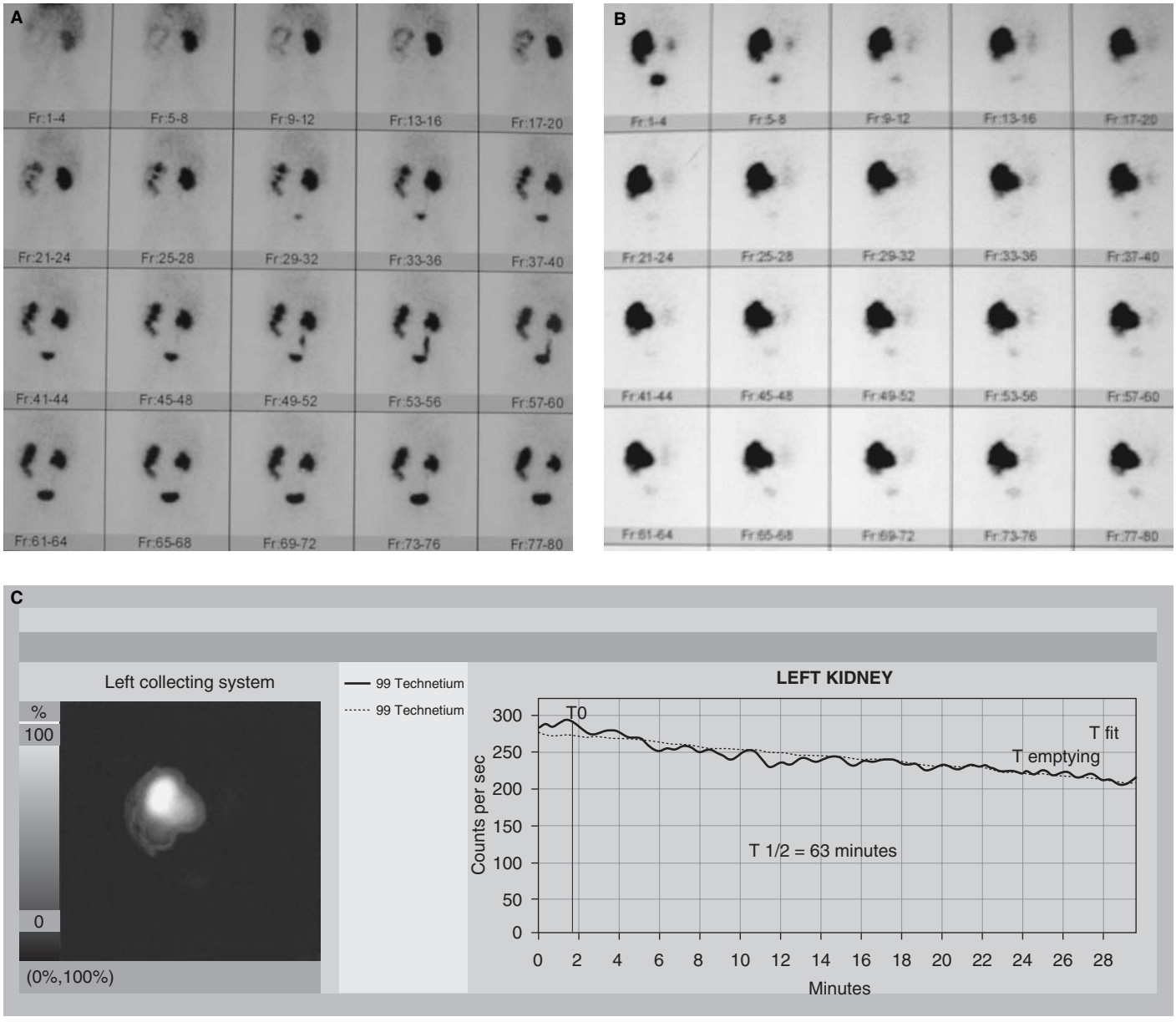


Figure 7.5 Left ureteropelvic junction obstruction, MAG3 renal scan. (A) Initial images showing tracer accumulation in a dilated left collecting system and normal clearance on the right. (B) Post-Lasix images showing poor drainage from left collecting system. (C) Prolonged half-time of left collecting system and slow washout as seen on time–activity curve.

Indirect (intravenous) radionuclide cystography

Indirect radionuclide cystography is another method for the detection of VUR which does not require bladder catheterization. This technique utilizes an intravenously injected radionuclide, ^{99m}Tc-DTPA or ^{99m}Tc-MAG3, and a conventional renal scan is obtained. The bladder continues to fill and the patient is instructed not to void. Once the renal collecting systems have emptied and most of the tracer is in the bladder, the patient is then instructed to void and dynamic images are obtained during voiding.

Although this technique obviates the need for catheterization and provides renal functional information, only VUR that occurs during voiding is detected. Also, the radiation dose is higher than that from the direct RNC. Success of indirect RNC depends on adequate renal function, rapid clearance of tracer from the upper tracts, urinary continence, and the ability of the

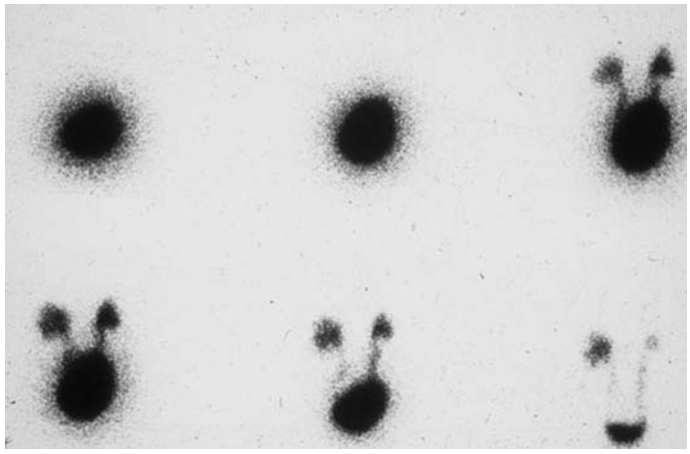


Figure 7.6 Nuclear cystogram demonstrating moderate bilateral reflux to both collecting systems.

patient to void upon request. Thus, this method is not suitable for children with decreased renal function, or those who are not toilet-trained. Comparative studies using DTPA have shown that the indirect RNC is not as sensitive as the direct RNC in detecting VUR.[30] This is especially the case with the lower grades of reflux. The use of ^{99m}Tc-MAG3 for indirect cystography has not increased the sensitivity for the detection of reflux.[31]

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8 Renal biopsy

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Renal biopsy is an important tool for establishing the morphologic diagnosis, prognosis, as well as guiding therapy of renal disease in children and adults. Although a renal biopsy can be performed by an open surgical procedure, the percutaneous method is the preferred manner of obtaining the renal biopsy sample in most children. Although percutaneous renal biopsy of palpable tumors was first performed in 1934 by Ball, its use for the diagnosis of medical disease was introduced by Iversen and Brun in 1951.[1,2] Since then, the technique has been continuously enhanced by better guidance and instruments. The advent of real-time ultrasound and automated biopsy needles during the last two decades has simplified the procedure and further improved its success and safety.[3]

Indications for renal biopsy

Renal biopsy is indicated to establish the morphologic nature of the renal disease and to predict prognosis and disease evolution, as well as in developing the appropriate therapy plan. Renal biopsy may also be utilized to monitor the response to therapy and the disease progression. Renal biopsy has been reported to influence the management of the disease state in as many as 42% of cases undergoing the procedure.[4]

A common indication for renal biopsy in children is poorly responsive nephrotic syndrome. Corticosteroid responsive nephrotic syndrome in children is considered to be due to minimal change disease, and a renal biopsy is not necessary in such patients.[5] A diagnostic renal biopsy is generally considered in patients with corticosteroid-non-responsive, or corticosteroid-resistant nephrotic syndrome, and where an underlying glomerulonephritis is suspected.[5,6] Focal segmental glomerulosclerosis (FSGS) can be a common form of glomerulonephritis in such patients.[7] Persistent, non-orthostatic proteinuria may be indicative of an underlying primary glomerulonephritis, such as FSGS, membranous glomerulonephritis (MGN), or membranoproliferative glomerulonephritis (MPGN). Renal biopsy is commonly performed for histologic diagnosis of these proteinuric disorders.

Another common indication for renal biopsy is persistent isolated hematuria, when the diagnosis of IgA nephropathy (Berger disease), Alport's syndrome, or thin basement membrane disease is being considered.[6] Renal biopsy is also indicated in children with acute glomerulonephritis who exhibit a rapidly progressive clinical course. Renal biopsy in such cases needs to be considered as an urgent diagnostic procedure and to guide therapy. Renal biopsy is generally not considered in patients with well-established acute postinfectious glomerulonephritis.

Renal biopsy can be of immense diagnostic value in patients with acute renal failure, where intrinsic renal diseases such as rapidly progressive glomerulonephritis, interstitial nephritis, and vasculitis are being considered. In most cases with acute renal failure of hemodynamic or nephrotoxic origin, a renal biopsy is generally unnecessary. In children with chronic renal insufficiency of unknown etiology, a renal biopsy is indicated to establish the underlying etiology. This is especially helpful in predicting the risk of recurrence of the original disease after renal transplantation. However, in advanced renal disease, the kidneys may be small, and densely echogenic and a renal biopsy may show only atrophic renal tissue and glomerulosclerosis, 'end-stage kidney'.

Renal biopsy is routinely used for the evaluation of renal transplant allograft dysfunction, which may be due to acute and chronic allograft rejection, drug toxicity, recurrence of original disease, or de-novo renal disease. Protocol renal allograft biopsies are useful for the diagnosis and post-treatment monitoring of acute rejection and for the surveillance of chronic allograft nephropathy.[8] Table 8.1 lists indication for renal biopsy.

Table 8.1 Indications for renal biopsy in children

Absolute indications
- Steroid-resistant nephrotic syndrome
- Persistent, non-orthostatic proteinuria
- Persistent glomerular hematuria
- Atypical or non-resolving acute glomerulonephritis
- Rapidly progressive glomerulonephritis
- Acute renal failure with nephrotic/nephritic syndrome
- Systemic diseases with renal involvement (vasculitis, metabolic diseases like Fabry disease)
- Renal allograft dysfunction
- Chronic renal failure of unknown etiology

Relative indications
- Monitoring response to therapy
- Monitoring drug nephrotoxicity
- Protocol biopsies of renal allograft

Contraindications to percutaneous renal biopsy

Percutaneous renal biopsy is an invasive, elective procedure, with well-defined risks. Absolute contraindications are those situations where the risks are extraordinarily high. Relative contraindications are those conditions that directly affect the safety of the procedure, or increase the level of difficulty and thereby indirectly increase the risk of complications. The physician must balance the benefits and risks of the procedure in each patient and decide if the procedure is indicated. An open surgical diagnostic renal biopsy may be considered if the patient has well-established contraindications to the percutaneous procedure. Table 8.2 lists absolute and relative contraindications for percutaneous renal biopsy.

Table 8.2 Contraindications to percutaneous renal biopsy

Absolute contraindications
- Uncontrolled coagulation abnormalities
- Uncontrolled severe hypertension
- Uncooperative patient
- Solitary kidney (not transplant)
- Acute pyelonephritis

Relative contraindications
- Severe azotemia/end-stage renal failure
- Anatomic abnormalities of the kidney
- Coagulopathy
- Concurrent use of drugs affecting coagulation (e.g. aspirin, dipyridamole)
- Chronic pyelonephritis
- Concurrent urinary tract infection
- Tumors
- Pregnancy
- Extreme obesity

Preparing the patient

Adequate preparation for the renal biopsy is the key for a successful and safe procedure. It should start with a thorough prebiopsy evaluation consisting of four elements: history taking, physical examination, laboratory evaluation, and ultrasonographic evaluation of the kidneys. Important elements of the history are bleeding diathesis (personal or family history); allergies to agents used during the renal biopsy; use of aspirin, nonsteroidal anti-inflammatory drugs, or other anticoagulation therapy; and a history of severe hypertension. Key elements of the physical examination are blood pressure evaluation, biopsy site assessment, and assessment of anatomic abnormalities that may interfere with imaging or positioning the patient during the biopsy. Laboratory evaluation should include a complete blood count and platelet count, biochemical profile, coagulation profile, and urinalysis. A complete ultrasonographic evaluation of the kidneys should be done in advance, to evaluate for anatomic abnormalities that might constitute absolute or relative contraindication for a percutaneous renal biopsy.[3]

The procedure needs to be scheduled in advance in order to assure a collaboration of the teams involved (nephrology, ultrasonography, pathology). Depending, on the institutional practices and prevailing patient needs, the patient may be admitted overnight prior to the procedure or come on the morning of the procedure. Medications that may affect coagulation must be interrupted for an appropriate duration in order to assure a safe procedure. The patient must be instructed to take nothing by mouth (NPO) for 6 hours prior to the biopsy.

The renal biopsy procedure is generally performed in a radiology procedure room that is appropriate for anesthesia and conscious sedation support. Current clinical practice is to guide the renal biopsy with a real-time ultrasound probe. This requires the help of a renal ultrasound technician in the procedure. The pathology department must be notified in advance so the biopsy specimen can be processed in a timely fashion. An intravenous access is placed before the procedure and maintenance intravenous fluids appropriate for age are provided. An informed consent, appropriate for the patient's age, needs to be obtained prior to the procedure. The type of sedation as well as the premedication varies according to institutional protocol. A young or uncooperative patient may require general anesthesia. This is prearranged with the anesthesiologist. Continuous cardiorespiratory monitoring should be started before the procedure and continued until the recovery phase. In the absence of any complications, patients are returned to their rooms for postbiopsy care. Table 8.3 provides suggested prebiopsy orders.

Table 8.3 Prebiopsy order sheet

- Admit patient
- Obtain consent for the procedure
- Patient to take nothing by mouth (NOP) for 6 hours – or as appropriate for conscious sedation/anesthesia
- Send and follow results for:
  - Complete blood count with platelet count
  - Basic metabolic panel
  - Coagulation profile (PT, PTT)
  - Bleeding time, only if clinically indicated
  - Urinalysis
- Type and hold one unit of packed red blood cells
- Place an intravenous line
- Start intravenous maintenance fluids
- Transport the patient, accompanied by nurse and with continuous cardiorespiratory monitoring, to the procedure room or the operating room

Biopsy imaging

Since the introduction of the percutaneous renal biopsy more than 50 years ago, the safety and use of the procedure has been enhanced by the technologic progress in imaging and guidance instruments. Intravenous pyelography with fluoroscopy, the initial modality used to image the kidney for the biopsy, was largely replaced by ultrasound in the mid 1980s.[3,9] The 1990s witnessed the introduction of the ultrasound-guided biopsy devices.[10,11]

Biopsy instruments

Vim–Silverman needle

In the mid 1950s Kark and Muehrcke revolutionized the field by using a new technique for percutaneous renal biopsy.[12–14] Besides changing the patient's position from sitting to prone, they replaced the aspiration needle, used by Iversen and Brun,[2] with a Franklin-modified Vim–Silverman needle (Figure 8.1). Their technique increased the success rate of the biopsy from less than 40% to above 90%, and significantly decreased the associated morbidity.[3]

The Franklin-modified Vim–Silverman needle consists of a trocar, a fitting obturator, and a cutting needle with prongs. The trocar and the fitting obturator are introduced together into the renal cortex, after which the obturator is removed and the cutting needle with prongs is introduced through the trocar. The cutting needle is advanced into the renal parenchyma followed quickly by the trocar. While maintaining the relative position of its components, the biopsy needle is quickly removed. The biopsy core is collected between the prongs of the cutting needle. The Vim–Silverman needle is not disposable and has now been abandoned, as automatic biopsy needles have been developed.

True-Cut needle

The True-Cut needle (Figure 8.2) became popular in the late 1970s and 1980s. This was the first 'semi-automatic' disposable needle introduced for renal biopsy procedures. The True-Cut needle consists of a cutting needle encased in a trocar. The cutting needle slides into the trocar to a preset depth. The trocar and the cutting needle are introduced together into the renal cortex. Once in the renal tissue, the cutting needle is advanced rapidly into the renal parenchyma, followed by the trocar. The needle and trocar are removed together, and the biopsy core is collected from the cutting needle.

Spring-loaded automated biopsy devices

Automatic biopsy devices were introduced in the late 1980s.[15] Several variations of the automated devices are available for clinical use today (Figures 8.3–8.6). These devices, when used

Figure 8.1 Franklin-modified Vim–Silverman biopsy needle. The obturator (O) fits into the trocar (T). The cuttings prongs (CP) are shown separately.

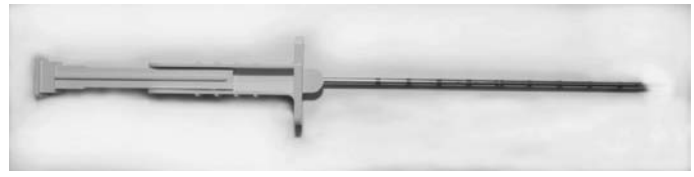

Figure 8.2 Disposable True-Cut biopsy needle (Baxter Health Care Corporation, Valencia, California).

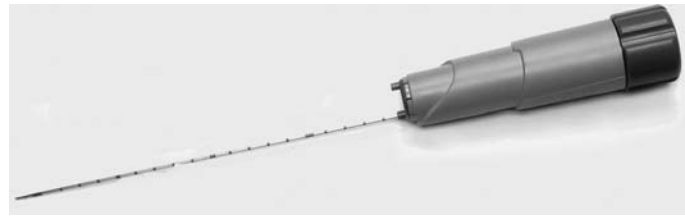

Figure 8.3 Bard Monopty biopsy instrument (CR Bard, Inc., Covington, Georgia).

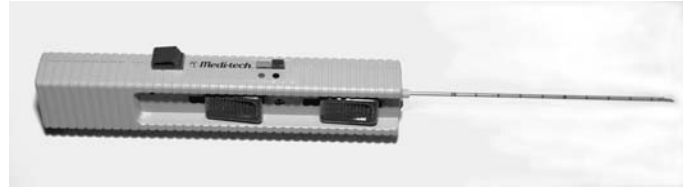

Figure 8.4 Meditech ASAP with Delta Cut biopsy system (Meditech Boston Scientific Corporation, Watertown, Massachusetts).

Figure 8.5 BioPince® full core biopsy instrument (Inter V, Gainesville, Florida). BioPince is a registered trademark of Medical Device Technologies, Inc.

Figure 8.6 Easy-Core biopsy needle (Boston Scientific Corporation, Natick, Massachusetts).

with real-time ultrasound guidance, have diminished the operator error and improved the success of the procedure.[3,16,17] The automated systems were initially semi-reusable (disposable needle and reusable spring-loaded device), but the currently available devices are fully automatic, for single use, and are disposable. The instrument consists of a trocar encasing a cutting needle; both are mounted on a spring-loaded handle. The needle is armed into the trocar, introduced until the renal cortex is reached, and then is advanced by releasing the loaded spring with the push of a button, or a release switch. One of the disadvantages of the automatic biopsy needles is that the length of the cutting core cannot be adjusted, making it hazardous to use these devices in very small infants, especially those with a thin cortical core. BioPince (see Figure 8.5) is the only commercially available biopsy needle that allows adjustment of the stroke length of the cutting core, from 13 mm to 33 mm.

Biopsy procedure

The patient is brought to the procedure room accompanied by a nurse and with continuous cardiorespiratory monitoring. The patient is placed in a prone position on the biopsy table, with a roll of sheets placed under the abdomen to stabilize and push the kidney towards the operator.[12,13] The lower pole of the left kidney, the optimal biopsy area, is localized by ultrasound and the corresponding point is marked on the skin on the back of the patient (Figure 8.7). The distance from the skin to the renal capsule is recorded from the ultrasound data. The anesthesiology support personnel give conscious sedation to the patient.

The biopsy area is prepped with povidone-iodine and draped. Local skin anesthesia is done with 1% lidocaine. A spinal tap needle is used to anesthetize the biopsy tract and to confirm orientation of the biopsy needle by ultrasound. A small incision of the skin, sufficient to allow the passage of the biopsy needle, is made using a scalpel. Under real-time ultrasound guidance, the biopsy needle is introduced and advanced, using the recorded angle and length of passage, until it reaches the outer kidney cortex. The patient is instructed to hold the breath and a maneuver to obtain the core of tissue is performed (dependent on the biopsy instrument used). The biopsy needle containing the tissue core is quickly removed.

The biopsy tissue obtained is immersed in normal saline and observed under a dissecting microscope for quality and glomerular content. Usually two cores are sufficient to obtain

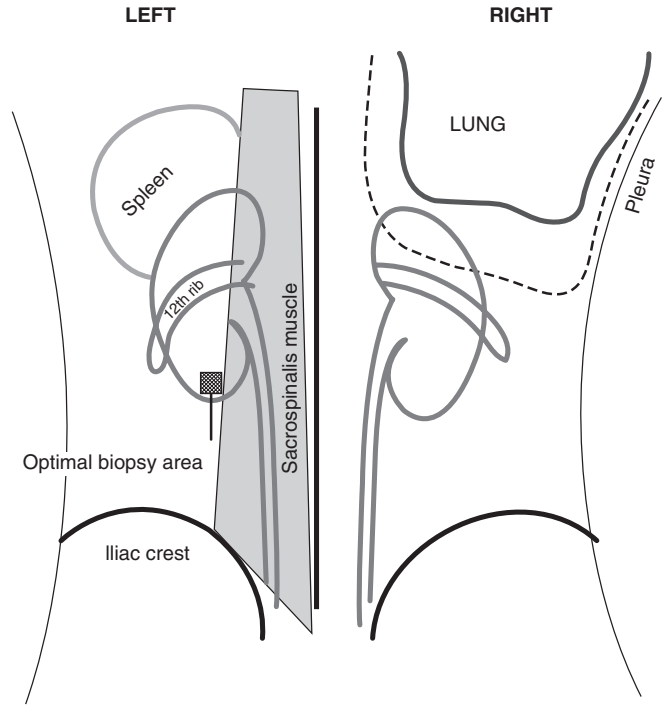

Figure 8.7 Diagram showing landmarks for localization of renal biopsy site in the left kidney.

an appropriate biopsy sample. A successful renal biopsy should have at least 20 glomeruli. The biopsy core is then divided and prepared for light microscopy, immunofluorescence, and electron microscopy.

Biopsy in a renal transplant

The presence of a single kidney in the renal transplant is not a contraindication for percutaneous renal biopsy. The kidney allograft is usually located in an anterior position, in the right or left lower quadrant, and is easily palpable. In preparation for the procedure, the patient is placed in the supine position. Depending on the position, usually the upper pole is located by ultrasound, marked on the skin, and the depth from skin to the renal capsule is recorded. The rest of the procedure is essentially identical to native renal biopsy. One needs to be cautious because the fibrous tissue (capsule) around the kidney allograft can be more difficult to penetrate. An open biopsy is generally indicated if the kidney allograft is located in an unusual/inaccessible position. In highly experienced centers, percutaneous renal biopsies of allografts placed extraperitoneally or intraperitoneally have been reported to have similar complication rates.[18]

Postrenal biopsy care

Once the percutaneous renal biopsy is completed, the kidney may be examined by ultrasound in search for any hematoma.

This examination may be postponed or repeated later in appropriate cases to increase the chance of detecting a hematoma.[3] Once the ultrasound is completed, the skin is cleaned with povidone-iodine and a pressure dressing is applied. The patient is positioned on the back and transported to an observation area, accompanied by a nurse and with continuous cardiorespiratory monitoring.

The postbiopsy procedure observation orders should be instituted immediately, especially for monitoring the vital signs for any evidence of hypovolemia (Table 8.4). The observation period is needed for the immediate detection of any complications, particularly hemorrhage and anesthesia-related events. The length of postbiopsy hospital stay is debatable. There is evidence to point that a shorter observation period (8 hours) with same day discharge from the hospital is sufficient in selected patients and is more economical.[19–22]

Table 8.4 Postbiopsy order sheet

- Lie patient flat on the back for 6 hours without bathroom privileges
- Continuous cardiorespiratory monitoring until awake from sedation
- Monitor vital signs:
  - Every 15 minutes for 1 hour
  - Every 30 minutes for 2 hours
  - Every 1 hour for 4 hours
- Check biopsy site with each set of vital signs
- Inform physician if changes outside set parameters, back pain, abdominal pain, active bleeding at the biopsy site
- Obtain hemoglobin/hematocrit at 4 hours postbiopsy
- Strict intake and output monitoring
- Inform physician if no urine output for 6 hours
- Check for macroscopic or microscopic hematuria and, if present, inform the physician
- Normal diet once the patient is awake; encourage oral fluid intake
- Discharge patient after (8–24 hours), if stable
- Follow-up in pediatric nephrology clinic in 1 week

Complications following renal biopsy

Complications following a renal biopsy can be separated into minor, major, and severe categories. While the incidence of minor complications are common, and may reach 100%, major complications have been reported in 5–10% of cases.[6] Severe complications are rare. Depending on the era of studies, the reported complication rate is variable. Most complications are the result of bleeding into the collecting system, with subsequent hematuria, or at the biopsy entry point into renal cortex, resulting in perinephric hematoma. Significant postbiopsy bleeding may occasionally result in drop in hematocrit, with need for transfusion and/or surgical intervention. Severe bleeding with the need for nephrectomy occurs extremely rarely. In a literature review of 19 459 percutaneous renal biopsies, need for nephrectomy was reported in 13 cases (0.06%).[23] Death directly attributable to renal biopsy is exceptionally rare, with a reported frequency of up to 0.08% in older reviews and 0.02% in the more recent reviews.[3,23] Tables 8.5 and 8.6 list complications associated with kidney biopsy.

Microscopic hematuria

Microscopic hematuria is the most common complication of renal biopsy, and occurs in almost all patients.[3] It usually resolves without any intervention and has no clinical significance.

Macroscopic hematuria

The incidence of macroscopic hematuria after native or allograft biopsies in children ranges from 2.7 to 26.6%.[22,24–36] Macroscopic hematuria is not usually clinically significant and resolves spontaneously within 24–48 hours. Rarely, macroscopic hematuria may produce a significant drop in hematocrit, with the need for transfusion. The need for an intervention (radiographical or surgical) to stop the bleeding is extremely rare. Infrequently, significant gross hematuria may result in formation of clots with subsequent urinary tract obstruction.[37–45] In most patients, observation and good intravenous hydration may be sufficient in preventing the formation of large clots.

Perinephric hematoma

The reported incidence of perinephric hematoma following renal biopsy is dependent on the modality of evaluation. Prior to the advent of ultrasound and computed tomography (CT), the reported incidence of clinically detectable perinephric hematoma was 1.4%.[46] It is now known that the incidence of perinephric hematoma, assessed by CT, is up to 91%.[3] Most perinephric hematomas are clinically insignificant and self-limiting. Caution should be used in transplant biopsies where significant subcapsular hemotomas may cause impairment of

Table 8.5 Complications following kidney biopsy

1. Minor
   - Microscopic hematuria
   - Macroscopic hematuria (transient)
   - Perinephric hematoma (not clinically significant)
2. Major
   - Macroscopic hematuria (requiring observation/intervention)
   - Perirenal hematoma (clinically significant)
   - Arteriovenous fistula
3. Severe
   - Need for a major surgical intervention
   - Death

Table 8.6 Incidence of complications following kidney biopsy

Complication	Incidence (%)	References
Microscopic hematuria	100	3
Macroscopic hematuria	2.7–26.6	22, 24–36
Urinary tract obstruction due to blood clots	0.5–5	37–45
Perinephric hematoma:		
• Clinical examination	1.4	46
• Ultrasound	6–70	3
• CT scan	57–91	3
Renal arteriovenous fistula	5–18	47–53
Clinically significant drop in hematocrit requiring blood transfusion	0.9–4.1	27, 31, 34, 36, 54
Nephrectomy for complications of renal biopsy	0.06	23
Death directly attributable to renal biopsy	0.02–0.08	3, 23

renal function with oligo-anuria.[55,56] Flank pain or abdominal pain may be encountered in some patients with a perinephric hematoma.

Arteriovenous fistula

Renal arteriovenous fistula is a well-recognized complication of percutaneous renal biopsy. The reported incidence of arteriovenous fistula following renal biopsy is 6–18%, as diagnosed by angiography, and 5–12%, as diagnosed by color Doppler ultrasound.[47–53] Development of hypertension, hematuria, and abdominal bruit after renal biopsy are clinical clues to the presence of an arteriovenous fistula. Most of these fistulas resolve spontaneously, but it is recommended that even small asymptomatic arteriovenous fistulas should be followed by color Doppler ultrasound.[3] Large symptomatic arteriovenous fistulas may need to be corrected by radiologic or surgical intervention.[3]

Miscellaneous complications

Infectious complications such as bacteremia, sepsis, perirenal abscesses, fistulas, and gastrointestinal tract injury as well as severe hemorrhage and death resulting from injury to the lumbar artery have been described.[40,54,57,58]

Concluding remarks

The technical advances in imaging and instruments have made the percutaneous renal biopsy a safe diagnostic procedure. Use of real-time ultrasound guidance and advanced instruments are the standard of care now. In spite of all the advancements, there are still a group of well-defined contraindications for a percutaneous renal biopsy, which the clinician must consider carefully. Finally, the success and safety of the percutaneous renal biopsy in children requires a knowledgeable and experienced pediatric nephrologist familiar with the technique.

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9 Hematuria and proteinuria

Marva Moxey-Mims

Hematuria and proteinuria are the two most common abnormalities in the urinalysis that lead to referral of children to pediatric nephrologists or urologists. Use of test-strips (dipsticks) to perform screening urinalysis in office practice has enhanced the rate of detection of these urinary abnormalities. Although isolated microscopic hematuria or low-grade proteinuria may not always be indicative of an underlying serious renal disease, when present together a detailed evaluation of the patient is necessary.

Hematuria

Although hematuria is a common manifestation of many disorders of the kidney and the urinary tract, its mere presence does not necessarily signal a progressive illness. The finding of isolated microscopic hematuria in children may be of minor clinical significance. Concern is, however, warranted when the hematuria is accompanied by proteinuria, hypertension, renal insufficiency, or physical abnormalities.[1,2]

Definition

By clinical description, hematuria can be isolated and asymptomatic, or associated with symptoms such as dysuria, abdominal pain, or systemic disease.

Gross hematuria

Hematuria is referred to as being macroscopic or gross when blood in the urine is visible to the naked eye. Depending on the site and type of renal or urinary tract disease, gross hematuria can be rusty, or tea colored pink, or frank red in color.

Microscopic hematuria

Microscopic hematuria is defined as ≥5 erythrocytes/HPF (high-power field) of a centrifuged urine specimen.[3] Microscopic hematuria is considered to be *persistent* if present in 2–3 urinalysis over a 2–3 week period.[1,2,4]

Detection

The urine test strips (or dipstick) used for detection of blood employ paper impregnated with *ortho*-toluidine buffered with organic peroxide. Hemoglobin in the urine, or in the red cells, catalyzes the oxidation of *ortho*-toluidine with peroxide to a blue color. The intensity of the color is evaluated against a color chart supplied by the manufacturer of the test strips to quantify the degree of hematuria.

The dipstick test detects heme molecules and is not specific for hematuria. A positive dipstick test could also indicate hemoglobinuria or myoglobinuria. Microscopic analysis and documentation of red blood cells in the urinary sediment will differentiate hematuria from these two pigmenturias. A false-positive dipstick result can occur if the urine sample is very concentrated, contains high concentrations of ascorbic acid, is contaminated with cleaning agents such as povidone-iodine or hypochlorite, or has microbial peroxidase. Red discoloration of urine, suggestive of gross hematuria, can also result from certain medications, food or vegetable dyes, bilirubin, porphyrins, or inborn errors of metabolism (Table 9.1)[5].

Epidemiology of hematuria

Gross hematuria is estimated to occur in 1.3/1000 children.[6] Persistent microscopic hematuria in two or more urine samples occurs in 1–2% of children between 6 and 15 years of age.[2]

Etiology of hematuria

The list of potential causes of hematuria is extensive, and the common causes in children are listed in Table 9.2. Urinary tract infection is the most common cause of hematuria in general practice.[6] The more serious diagnoses of acute glomerulonephritis and tumors of the urinary tract account for 4% and 1% of causes of hematuria, respectively.[6] Trauma (even minor trauma in cases of renal malformation), urolithiasis, and sickle cell disease/trait can also result in gross hematuria. When hematuria is accompanied by other urinary abnormalities, or systemic symptoms, the differential diagnosis includes glomerulonephritis,

Table 9.1 Causes of 'red' or dark-colored urine

Macroscopic hematuria
Myoglobinuria
Hemoglobinuria
Biologic pigments:
- Bilirubin
- Urates
- Melanin

Inborn errors of metabolism:
- Alkaptonuria
- Tyrosinosis
- Porphyrinuria

Drugs and food colors:
- Chloroquine
- Desferrioxamine
- Diphenylhydantoin
- Levodopa
- Methyldopa
- Metronidazole
- Nitrofurantoin
- Phenolphthalein
- Pyridium
- Rifampin
- Sulfa drugs
- Food/dyes
- Beets
- Blackberries

acute tubular necrosis, hypercalciuria, urinary tract infection, trauma, sickle cell disease/trait, tumors, and malformations.

Evaluation of hematuria

The aims of evaluation of hematuria in a pediatric patient are:

- to determine if it is glomerular (due to nephritis) or non-glomerular (or urologic)
- to conduct appropriate investigations to determine the underlying cause.

A thorough medical and family history, physical examination, and urinalysis with microscopic evaluation of the sediment are key to determining further investigative steps necessary for evaluation of hematuria.[7] Once the presence of red blood cells has been confirmed in the urine, a directed history and physical examination should take place (Table 9.3). Urinalysis, with microscopy of the spun urinary sediment, is helpful in determining whether the hematuria is glomerular or non-glomerular in nature.

Urine color

Generally, gross hematuria of glomerular origin is associated with a brownish, tea, or cola-colored urine, as opposed to the

Table 9.2 Etiology of hematuria

Glomerular hematuria
Acute glomerulonephritis
Chronic glomerulonephritis:
- IgA nephropathy
- Mesangali proliferative glomerulonephritis
- Membranoproliferative glomerulonephritis
- Focal segmental glomerulosclerosis
- Membranous nephropathy
- Systemic lupus erythematosus
- 'Shunt' nephritis
- Goodpasture's syndrome

Inherited nephropathies:
- Alport's syndrome
- Benign familial hematuria
- Nail-patella syndrome
- Fabry disease
- Polycystic kidney diseases
- Medullary cystic disease
- Congenital nephrotic syndrome

Hemolytic uremic syndrome
Henoch–Schönlein purpura
Minimal change disease
Systemic vasculitis
Diabetes mellitus
Amyloidosis

Non-glomerular hematuria
Urinary tract disorders:
- Urinary tract infection (bacterial, viral, parasitic)
- Urinary calculi
- Hypercalciuria
- Chemical cystitis
- Urethral/bladder foreign body
- Hydronephrosis
- Obstructive uropathy
- Urinary tract trauma
- Renal and urinary tract tumors
- Specific parasitic infections (schistosomiasis)

Tubulointerstitial diseases:
- Acute pyelonephritis
- Nephrocalcinosis
- Interstitial nephritis
- Nephrotoxins (including heavy metals, radiocontrast medium, analgesics, antiretrovirals)
- Tuberous sclerosis
- Acute tubular necrosis

Vascular disorders:
- Renal vein/artery thrombosis
- Malignant hypertension
- Nutcracker syndrome
- Loin pain hematuria
- Congestive heart failure

Hematologic disorders:
- Sickle cell trait/disease
- Coagulopathies

Table 9.3 Important aspects of history and physical examination in evaluation of hematuria

Patient history
Exercise
Menstruation
Trauma
Medication
Recent URI/impetigo
Dysuria/frequency/urgency
Suprapubic/abdominal/costovertebral angle pain
Myalgias/arthralgias
Stone passage
Timing of hematuria (throughout/initiation/termination of urine stream)
Family history
Chronic kidney disease
Hematuria
Deafness
Hypertension
Nephrolithiasis
Hemoglobinopathy
Coagulopathy
Physical examination
Hypertension
Fever
Edema
Rash
Arthritis
Costovertebral angle tenderness
Abdominal mass

URI, upper respiratory tract infection.

Table 9.4 Causes of hemoglobinuria and myoglobinuria

Hemoglobinuria
Hemolytic anemia
Mismatched blood transfusions
Mechanical erythrocyte damage (artificial cardiac valves)
Sepsis/disseminated intravascular coagulation (DIC)
Freshwater near drowning
Toxins:
• Carbon monoxide
• Lead
• Turpentine
• Phenol
• Naphthalene
Myoglobinuria
Rhabdomyolysis
Myositis
Severe muscle injury

pink or bright red color seen if hematuria is non-glomerular (urinary tract bleed or urologic hematuria) in origin. In a patient with visibly 'red' or dark-colored urine, but without evidence of blood on dipstick testing, other causes of urinary discoloration need to be ruled out (see Table 9.1). If the dipstick is positive for blood, but no erythrocytes are seen on microscopic examination, then hemoglobinuria or myoglobinuria need to be considered as the diagnostic possibilities (Table 9.4). The patient's history and physical examination are helpful in differentiating these two entities. Pallor and icterus are seen in hemoglobinuria, whereas a history of severe exercise, myalgia, and demonstration of muscle tenderness favor the diagnosis of myoglobinuria, but urine spectrophotometry is necessary for confirming the diagnosis.

Urine microscopy

Microscopic analysis of the spun urine sediment also helps to differentiate between glomerular and non-glomerular hematuria.[8–10] Glomerular hematuria results from disruption of the glomerular filtration barrier and that leads to the formation of dysmorphic erythrocytes, which are characterized by variable size and irregular outlines (Figure 9.1). Additional features of glomerular hematuria are proteinuria and red blood cell and granular casts. Non-glomerular hematuria, on the other hand, is characterized by eumorphic erythrocytes (uniform size and shape), a lack of casts, and often an absence of accompanying proteinuria.

Focused investigations of non-glomerular hematuria

Historical information is helpful in the diagnosis and possible localization of the site of lesions in non-glomerular or urologic hematuria. Hematuria associated with red or pink-colored urine throughout the act of urination is referred to as *total hematuria*. It usually arises from a source of bleeding in the bladder or at a higher anatomic level. *Initial hematuria* is a term used to indicate bleeding that occurs at the initiation of urination, sometimes as a distinct drop of fresh blood. The source of such hematuria is the penile urethra. Hematuria arising out of lesions in the posterior urethra, bladder neck, or trigone (base of the bladder) leads to hematuria at the end of urination, and is designated as *terminal hematuria*.

Urine culture should be obtained in all children with the diagnosis of non-glomerular hematuria to rule out urinary tract infection. A renal and bladder ultrasound should also be considered in these patients to rule out structural urinary tract anomalies, calculus disease, or tumors. Sickle cell status should be determined if hematuria is detected in an African-American child. Hypercalciuria is a common cause of non-glomerular microhematuria in children, and should be ruled out by measuring the calcium/creatinine ratio in a spot urine sample or 24-hour urine collection for a 'stone risk analysis'. In order to standardize our evaluation, we recommend obtaining a fasting, second morning urine sample for calcium excretion. A CAT scan and urinary 'stone risk analysis' will be necessary in patients with suspected or documented urolithiasis.

Referral to a urologist for cystoscopy is warranted if bladder pathology such as bladder hemangioma or a tumor of the bladder

or urethra is suspected as the cause of hematuria. Cystoscopy may also be helpful in localizing the site of gross hematuria to one of the ureteral orifices, so that further investigations can then be focused on that side.

Focused investigations of glomerular hematuria

Various glomerulonephritides can cause glomerular hematuria. Due to the concerns about long-term renal damage, chronic kidney disease (CKD), and hypertension, investigations and treatment should be expedited in these patients. A positive test for hematuria in parents can help to establish the diagnosis of a familial disorder such as benign familial hematuria or Alport's syndrome. With a positive family history of hematuria and renal failure, a hearing test should be done to assist in the diagnosis of Alport's syndrome.

Since postinfectious glomerulonephritis still occurs frequently in children, patients with glomerular hematuria should undergo a panel of tests to rule out this diagnosis (C3, ASO titer, and anti-DNAse B titer). Proteinuria should be quantified in all patients found to have glomerular hematuria: this can be achieved by determination of the protein/creatinine ratio in a spot sample of urine. In order to standardize our approach, we recommend that proteinuria be assessed in the first morning sample of urine when the patient wakes up. A diagnostic renal biopsy may be considered in patients when glomerular hematuria is associated with renal dysfunction, hypertension, and nephrotic syndrome. Flow diagrams of investigations in patients with gross and microscopic hematuria are shown in Figures 9.2 and 9.3, respectively.

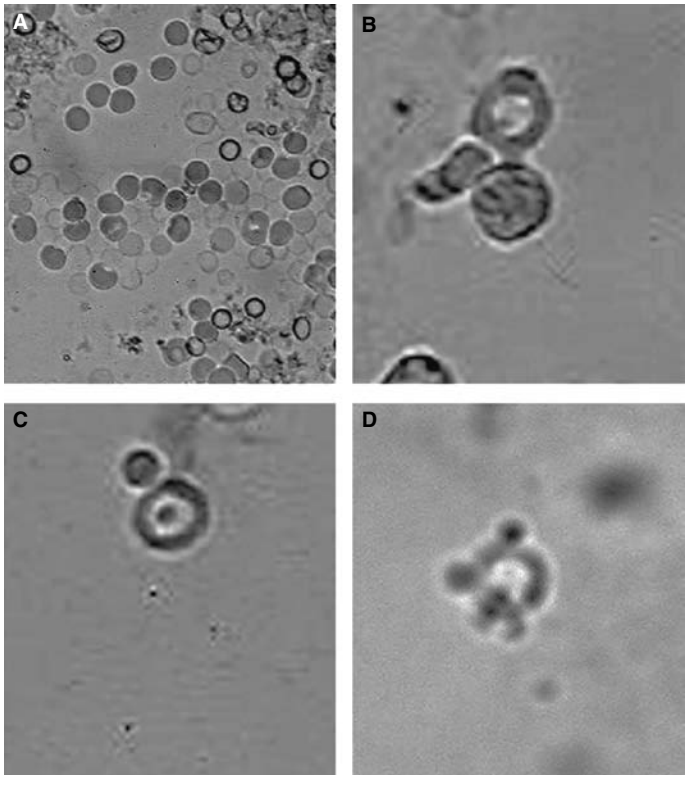

Figure 9.1 Red blood cell (RBC) morphology in hematuria. (A) Eumorphic RBCs: the cell outlines are smooth and hemoglobin is uniformly distributed in the cells. (B) Dysmorphic RBCs with a doughnut shape: the hemoglobin is marginated towards the periphery of the red cell. (C) Dysmorphic RBC with target shape: hemoglobin is marginated into the center and along the periphery of the RBC. (D) Dysmorphic RBC with irregular cell wall: margination of hemoglobin in these areas gives rise to the 'mickey mouse' RBC shape.

Proteinuria

Normal urinary protein excretion is approximately 150 mg/day in adults, which is used as a general ballpark figure for older children as well.[11] Urinary protein excretion is, however, variable in younger children. Table 9.5 lists the normal values of urinary protein excretion in children.

Glomerular capillary barrier

The glomerular capillary is a complex and selective filtration barrier that is made of three layers:

- endothelium with fenestrations
- glomerular basement membrane (GBM)
- the epithelial cells and the complex network of podocytes (Figure 9.4).

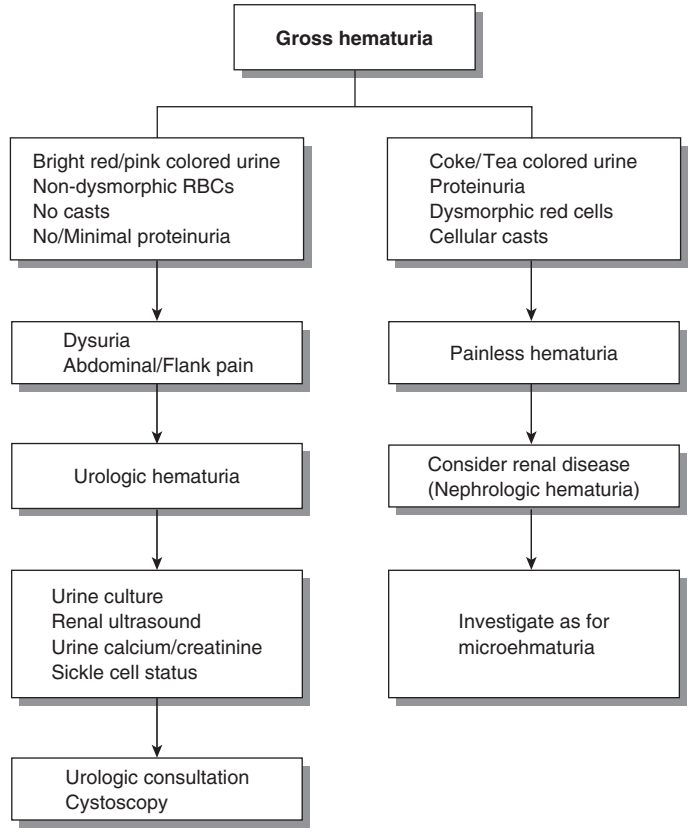

Figure 9.2 Algorithm for evaluation of gross hematuria.

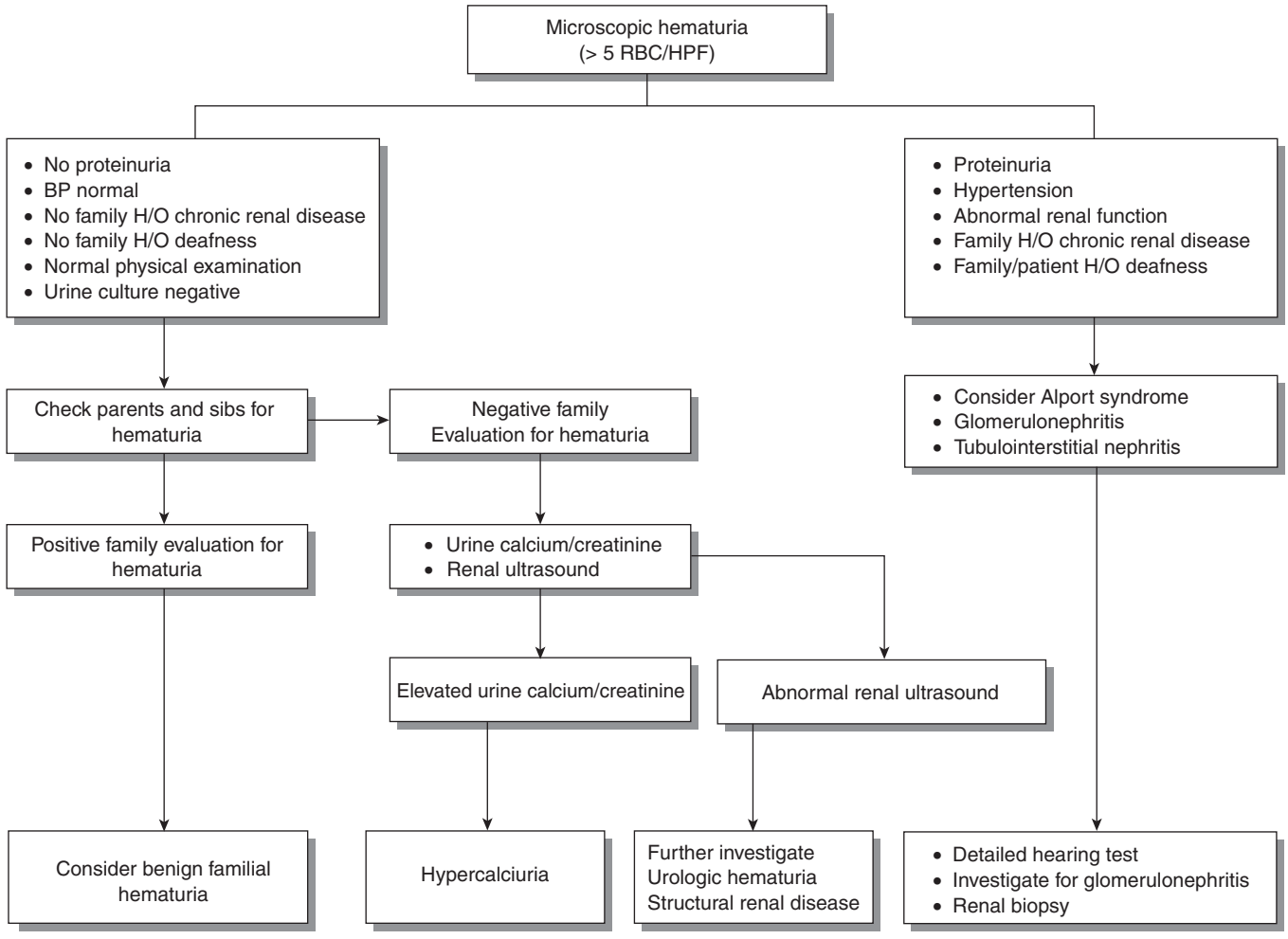

Figure 9.3 Algorithm for evaluation of microscopic hematuria.

Table 9.5 Normal 24-hour urinary protein excretion by age

	Total urinary protein excreted (mg)
Premature babies	14–60
Full-term babies	15–68
Infants	17–85
Children:	
2–4 years	20–121
4–10 years	26–194
10–16 years	29–238

Adapted from data in Reference 11.

The endothelial fenestrations (EF) are 70–100 nm in size and permit contact between plasma within the capillary lumen and the GBM. The endothelium is not believed to provide a significant barrier to transglomerular migration of fluid and macromolecules. The GBM, a gel-like acellular structure is composed of tightly woven type IV collagen, laminin, and heparin sulfate proteoglycans. Ultrastructurally, the GBM has three distinct layers, the thin lamina rara interna and lamina rara externa, with the lamina densa sandwiched in between.

The final barrier to the transcapillary passage of fluid and macromolecules is the epithelial cell. The epithelial cells are large, with specialized cytoplasmic extensions known as foot processes, which firmly anchor them to the GBM. The adjacent foot processes do not come into contact with each other and are separated by ~40 nm wide spaces known as filtration slits.[12] These slits are bridged by a continuous membrane-like structure known as the slit diaphragm (SD) (Figure 9.5).

Based on electron microscopy findings, Rodewald and Karnovsky proposed in 1974 that the SD consisted of a central filamentous structure running parallel to the surface of the podocytes and interdigitating extracellular processes running across in a 'zipper design' towards the adjacent podocyte.[13] The functions of the epithelial cell and its various extensions have remained a mystery until recently. Understanding of the structure and function of the podocytes and the SD has been

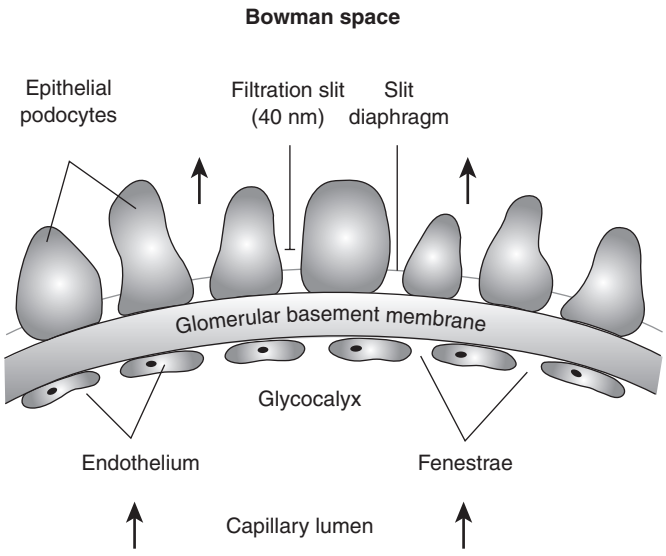

Figure 9.4 Conceptual representation of the glomerular filtration barrier. (Reproduced with permission from J Clinical Invest 114:1412, 2004.)

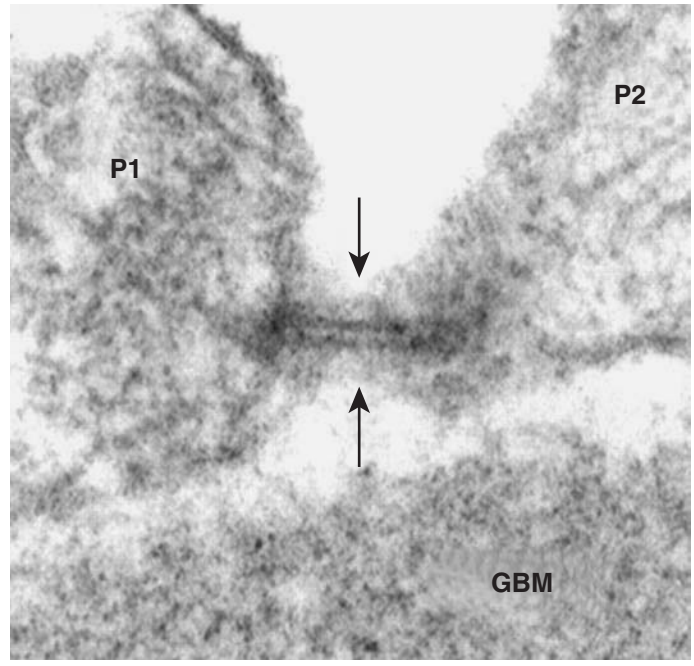

Figure 9.5 Electron micrograph showing a filtration slit with adjacent podocytes P1 and P2; double-layered slit diaphragm (arrows) bridges between the two podocytes, and the glomerular basement membrane (GBM). (Reproduced with permission from J Clin Invest 114:1475–1483, 2004.)

exponentially advanced in the last decade. Discovery of several key proteins that localize to the SD and the podocytes has provided an understanding of the function of the podocytes and the SD. These proteins include nephrin and podocin.[14]

Nephrin has been proposed to be one of the molecules that extend as an extracellular rod-like structure from the foot processes. Nephrin from the two adjacent foot processes meet in the middle of the fenestration to form the zipper-like structure of the SD proposed by Rodewald and Karnovsky.[15,16]

The SD plays an important role in providing selective permeability characteristics for the glomerular capillaries. Indeed, abnormalities in specific proteins present in the SD caused by inherited gene mutations result in specific clinical disorders associated with proteinuria. Of these, mutation in the nephrin gene NPHS1, which results in the Finnish type of congenital nephrotic syndrome, was the first one to be described.[17]

Macromolecular transport through GBM

Despite the complex structural attributes of each component of the glomerular capillary wall, it functions as a single filtration unit. Plasma ultrafiltrate and macromolecular transport through the GBM, including that of plasma proteins, is influenced by molecular size, shape, and charge. Passage of glomerular ultrafiltrate is thought to occur across the GBM, through the SD and extracellular spaces of the epithelial cell, and into the urinary space of the Bowman capsule.

The glomerular filter does not allow free passage of macromolecules, and its function as a selective barrier is well characterized. Using neutral dextran and other single macromolecular species of uniform shape, it has been shown that the glomerular passage of molecules is increasingly restricted as the molecular size increases beyond 20 Å. Albumin, which has a molecular size of 36 A, is almost completely prevented from passing through the glomerular capillary barrier. At a molecular size of 42 Å, there is almost no clearance of molecules from the glomerular capillaries. As a result, none of the high molecular weight (HMW) proteins, such as IgG, IgM, and α_2-macroglobulin, are allowed passage by the glomerular filtration barrier. On the other hand, low molecular weight (LMW) proteins, such as β_2-microglobulin (molecular size 11.8 Å), and immunoglobulin light chains are filtered readily.[12]

In addition to molecular size, molecular charge has also been shown to influence the clearance of macromolecules from the glomerular capillary. In comparison with neutral dextran, cationic dextran has a higher glomerular clearance and anionic dextran has reduced glomerular clearance. Similar results have been obtained with other molecular markers. This has led to the concept that the passage of anionic molecules such as plasma proteins is actively hindered by the anionic surface charge of the glomerular filter.[12]

Tubular metabolism of filtered protein

The glomerular filtrate reaching the proximal tubule contains mostly filtered LMW proteins and minor amounts of albumin (1–3 mg/dl). Therefore, in an adult with a glomerular filtration rate (GFR) of 125 ml/min, or 180 L/24 hours, the total amount of albumin filtered is 1800–5400 mg/day. However, normal urinary protein excretion under physiologic circumstances in an

adult is <150 mg/24 hours, suggesting that tubular processing reabsorbs most of the filtered albumin. Histochemical and ultrastructural investigative techniques have established that proteins are reabsorbed primarily in the proximal tubular cells by a process of endocytosis. After internalization, the endocytosed protein vesicles fuse with the lysosomes, where the proteins undergo hydrolysis.[18,19] Cubilin and megalin, two membrane proteins present on the surface of the proximal tubular cells, appear to have a key role in the transport of ultrafiltered proteins from the tubular lumen into the cell cytoplasm.[20] Congenital cubilin deficiency, or Gräsbeck–Imerslund disease, is associated with proteinuria.[21] Cationic proteins are more avidly bound to the tubular receptor transport mechanisms and are removed more efficiently from the glomerular ultrafiltrate in the proximal tubules than non-cationic proteins.[22]

Types of proteinuria

The source of urinary protein excretion can be divided into three categories: glomerular proteinuria, tubular proteinuria, and overflow proteinuria.

Glomerular proteinuria

Proteinuria resulting from diseases of the glomerular ultrafiltration barrier (minimal change, other glomerulonephritides) is referred to as glomerular proteinuria. Glomerular proteinuria is detected by most clinically used tests, including dipsticks.[23] Urine protein electrophoresis (UPEP) analysis of glomerular proteinuria shows a pattern similar to serum protein analysis, with albumin constituting a dominant fraction (Figure 9.6A).

Tubular proteinuria

Many inherited tubulopathies (e.g. Fanconi syndrome) and acquired tubular disorders (e.g. nephrotoxins) are characterized by a failure to reabsorb the LMW proteins from the glomerular ultrafiltrate. Proteinuria seen in such clinical circumstances is referred to as *tubular proteinuria*.[24] In contrast to glomerular proteinuria, the standard urinary dipstick method utilized in urinalysis does not detect LMW proteins. Therefore, specific analytical methods are necessary to uncover tubular proteinuria. Three markers commonly used as indicators of tubular proteinuria in clinical practice are β_2-microglobulin, α_1-microglobulin, and retinol-binding protein.[25] UPEP in tubular proteinuria demonstrates α and β globulin peaks, with albumin forming only a minor fraction of the total protein excretion (Figure 9.6B). LMW proteinuria has recently been suggested to be a more reliable predictor of outcome in chronic glomerular disease when compared with total daily urinary protein excretion.[26]

Overflow proteinuria

Overflow proteinuria is the least common type of proteinuria found in children. Monoclonal gammopathies characterized by high plasma concentrations of monoclonal immunoglobulin fractions in the serum lead to elevated concentrations of these LMW proteins in the glomerular ultrafiltrate. Once the proximal tubular reabsorption capacity of these filtered plasma proteins is exceeded, they begin to appear in the urine. Such proteinuria is known as *overflow proteinuria*. Bence Jones protein, which is seen in multiple myeloma and other B cell lymphomas, is an example of such overflow proteinuria. Bence Jones protein was originally detected by heat precipitation methodology, but immunoelectrophoresis is now generally used to detect the monoclonal (M peaks) urinary protein excretion.

Tamm–Horsfall protein

Another component of normal urine that has attracted attention recently is the glycoprotein called Tamm–Horsfall protein (THP), or uromodulin. THP constitutes 50% of the urinary protein excretion in normal subjects, and is produced by

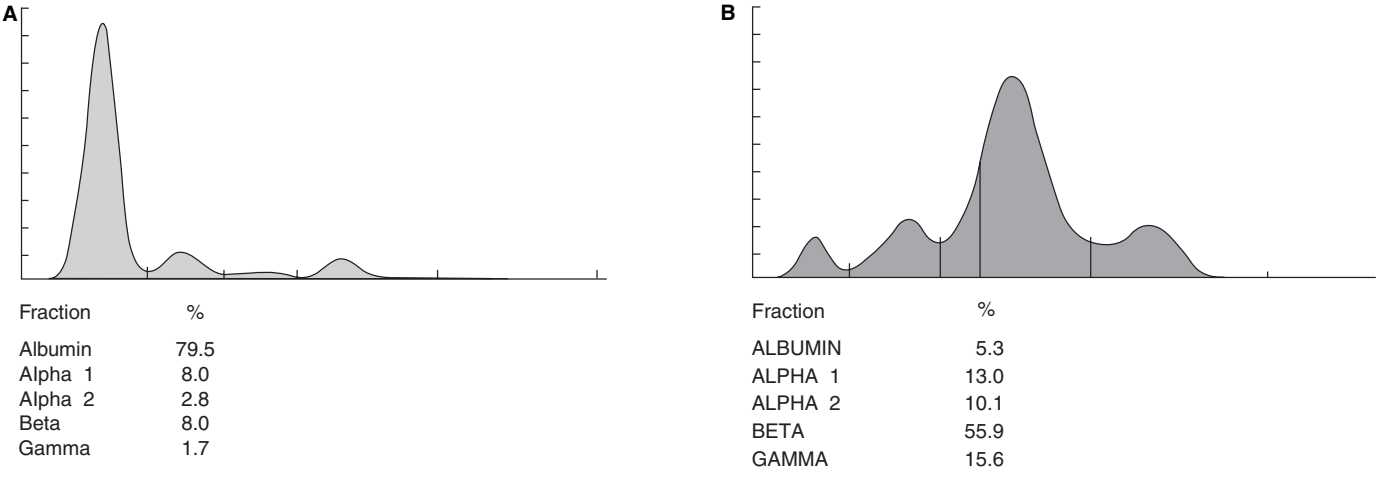

Figure 9.6 Urine protein electrophoresis (UPEP). (A) Patient with glomerular proteinuria: of note is the large albumin peak. The UPEP pattern is similar to the plasma electrophoresis pattern. (B) Patient with tubular proteinuria: the globulin peaks dominate in this type of proteinuria.

the cells of the thick ascending loop of Henle and early distal convoluted tubule.[27] THP is not detected by the routine urinalysis techniques and is measured by immunoassay or high-performance liquid chromatography (HPLC).

The role played by THP under physiologic conditions is not fully clear. THP may play a protective role against urinary tract infections by binding to *Escherichia coli*,[28] and it may also protect against stone formation.[29] THP forms the matrix of hyaline and other urinary casts. Because of its affinity for binding hemoglobin and immunoglobulin chains, and the property of gelation and aggregation, THP has been considered to play a role in the pathogenesis of pigment nephropathy, as well as cast nephropathy associated with multiple myeloma.[30] THP has also been implicated in the pathogenesis of tubulointerstitial nephritis, but the role is less certain than previously thought.

Quantification of proteinuria

Dipstick test

The urinary dipstick examination for proteinuria is a convenient method for detection of proteinuria. This method is able to provide a semiquantitative estimate of the degree of proteinuria. The test is affected by the urinary concentration and pH. Concentrated urine may give a positive reading even when the daily protein excretion is normal, whereas a dilute urine may result in a negative, or only slightly positive reading even in the presence of elevated daily protein excretion. False-positive results may also occur if the urine is highly alkaline, and false-negative results can be seen in the presence of high levels of ascorbic acid. Sulfosalicylic acid precipitation of protein can provide a semiquantitative estimation of urinary protein excretion that is not affected by pH or ascorbic acid.

Timed collection

The 'gold standard' of urinary protein quantitation is the measurement of protein in a carefully timed urine collection, usually over 24 hours. Calculation of the *creatinine excretion index* in the collected urine is often employed by nephrologists to judge the completeness of the collected 24-hour urine sample. The creatinine excretion index, or creatinine excretion per kilogram of body weight (total urinary creatinine/patient's weight), should be 15–20 mg/kg/24 hours for the urine collection to be considered adequate.

Protein/creatinine ratio

Since collection of timed urine is often difficult in children, an acceptable alternative is the measurement of the urine protein/creatinine ratio in a spot sample of urine.[31,32] A protein/creatinine ratio of ≤0.2 mg/mg is considered normal in children older than 2 years, while a ratio of ≤0.5 is considered normal in those younger than 2 years of age. The protein/creatinine ratio as a measure of urinary protein excretion has been validated in adults as well as in children.[31,32] An approximate value of the 24-hour urinary protein excretion (mg/m^2/day) can be obtained by multiplying the urine protein/creatinine ratio by 0.63.[33] The protein/creatinine ratio has been shown to be superior to a measurement of the protein/osmolality ratio.[34]

Quantification of urinary albumin has been a matter of debate recently. Conventional immunoassays may not be able to quantify all of the albumin present in urine, since non-reactive or non-immunogenic albumin may not be assayed.[35,36] Research efforts are underway to develop better analytical methods to quantitate total albumin, which can be used to predict renal disease in early stages.

Selectivity of proteinuria

Selectivity of proteinuria index (SPI) was introduced in the early 1960s as a test to predict the outcome of nephrotic syndrome.[37] SPI compares the fractional excretion of a LMW protein such as albumin (MW 60 000) or transferrin (MW 90 000) with a HMW protein such as immunoglobulin G (IgG, MW 160 000). Highly selective proteinuria correlates with diseases associated with good clinical outcome, such as minimal change disease. Intermediate or poorly selective proteinuria is predictive of poor clinical outcome.

$$\text{SPI} = \frac{\text{Urine IgG}}{\text{Serum IgG}} \times \frac{\text{Serum transferrin}}{\text{Urine transferrin}} \times 100$$

Highly selective proteinuria : SPI ≤ 0.10
Moderately selective proteinuria : SPI ≥ 0.11 ≤ 0.20
Poorly selective proteinuria : SPI ≥ 0.21

As renal biopsy techniques became available for investigation of nephrotic syndrome and direct correlation of pathology with outcome was established, the value of SPI became less evident. However, some emerging recent data have shown that SPI may be a useful tool in evaluating patients with proteinuria, especially if more modern methods of protein assay are applied. A stronger predictor of outcome of proteinuric disorders has been shown by using a larger molecular marker, IgM, instead of IgG.[38] Bazzi and colleagues found that SPI correlated well with interstitial disease present in patients with proteinuric disorders.[39] However, since considerable over lap exists between results from different clinical groupings, SPI should be considered to be an adjunctive test.

Epidemiology of proteinuria

The prevalence of proteinuria in children is 5–6%, with an incidence of 1–5%.[3,40,41] Proteinuria occurs more often in adolescents, and is more common in girls.[3]

Etiology of proteinuria

Artifactual proteinuria can result from vulvovaginitis, urethritis/prostatitis, and contamination by menstrual blood. Transient proteinuria can be seen after exercise, dehydration, or fever.[40,42–44] Orthostatic proteinuria is a common condition encountered in older children and adolescents and is discussed

below in detail. Persistent proteinuria is a manifestation of nephrotic syndrome and can be an important clue for acute or chronic glomerulonephritides and interstitial nephritis. Table 9.6 lists the causes of proteinuria.

Table 9.6 Causes of proteinuria

Artifactual
Vulvovaginitis
Infections
- Non-sexually transmitted
- Sexually transmitted diseases
- Fungal infection

Foreign body
Contact irritation
Menstrual blood contamination
Urethritis
Prostatitis

Glomerular diseases (see also Table 9.2)
- Nephrotic syndrome
- Glomerulonephritis
- Hypertension
- Diabetes mellitus
- HIV nephropathy

Tubular diseases – inherited
- Cystinosis
- Wilsons disease
- Lowe syndrome

Tubular diseases – acquired
- Interstitial nephritis
- Reflux nephropathy
- Acute tubular necrosis
- Heavy metal poisoning

Non-pathologic proteinuria
- Orthostatic proteinuria
- Fever
- Exercise

Evaluation of proteinuria

History

A thorough history, physical examination, and urinalysis are necessary. The essential historical aspects to be established are the duration of documented proteinuria, presence of any symptoms of nephrotic syndrome, history of any drug intake or exposure to toxins, and evidence of any primary collagen vascular disorder characterized by rash, fever, joint pains, or any pulmonary symptoms. Family history of any renal disease needs to be ascertained in order to determine if inherited disorders such as Alport's syndrome need to be considered.

Physical examination

The purpose of a physical examination is to establish a baseline state of health, including blood pressure, evidence of edema, and any clinical manifestations of rash that may be indicative of vasculitis or collagen vascular diseases. The respiratory system, including the sinuses, should be looked at for any evidence of clinical disease, sinusitis, or polyps.

Laboratory studies

Once proteinuria has been confirmed, and if it is isolated (i.e. no other urinary abnormalities), the first step should be evaluation for possible orthostatic proteinuria (see below). If orthostatic proteinuria is ruled out, the next steps are a directed set of laboratory tests, based on the results of the history and physical examination (Figure 9.7). If hematuria is present along with proteinuria, evaluation should proceed along the lines previously indicated for a patient with the combination of hematuria and proteinuria (see Figure 9.3).

Orthostatic proteinuria

Orthostatic, or postural proteinuria, is seen in about 60% of children evaluated for proteinuria.[45] Orthostatic proteinuria is characterized by mild, selective proteinuria that is seen only when the subject is upright. It is generally seen in preteens, teenagers, and young adults.

Pathogenesis

The cause of orthostatic proteinuria is unknown. Several studies have noted compression of the renal vein, or *nutcracker phenomenon*, in patients with orthostatic proteinuria.[46,47] One case report has shown that the urine obtained from the ureter of the kidney involved in venous compression is responsible for abnormal urine protein excretion. In an interesting report from Devarajan, a renal transplant donor was found to have orthostatic proteinuria.[48] At surgery the left kidney (donor kidney) was noted to have a kink in the renal vein. After nephrectomy, the orthostatic proteinuria resolved completely. The recipient of the kidney also has no evidence of proteinuria. The inference drawn is that a kink in the left kidney was responsible for venous compression on that side and the resultant orthostatic proteinuria.

In one study, renal biopsy in 12 patients with well-documented orthostatic proteinuria showed a subtle and focal increase in mesangial matrix, and deposition of C3 complement and IgG was seen in 10 of the 12 patients.[49] Electron microscopy was normal in 11 of the 12 cases and foot-process fusion was noted in one patient. Although no clear histologic criterion was diagnostic of postural proteinuria, the authors speculated that the presence of C3 in blood vessels might indicate some form of glomerulonephritis. Devarajan has presented an integrated hypothesis that an exaggerated renin–angiotensin response in the upright posture could be the trigger for proteinuria in these individuals, and that an underlying subtle glomerular pathology may be a predisposing factor as well.[48]

Diagnosis

The diagnosis of orthostatic proteinuria employs a simple test. The principle of the test is to document proteinuria in the upright position, and its absence in recumbence. One can

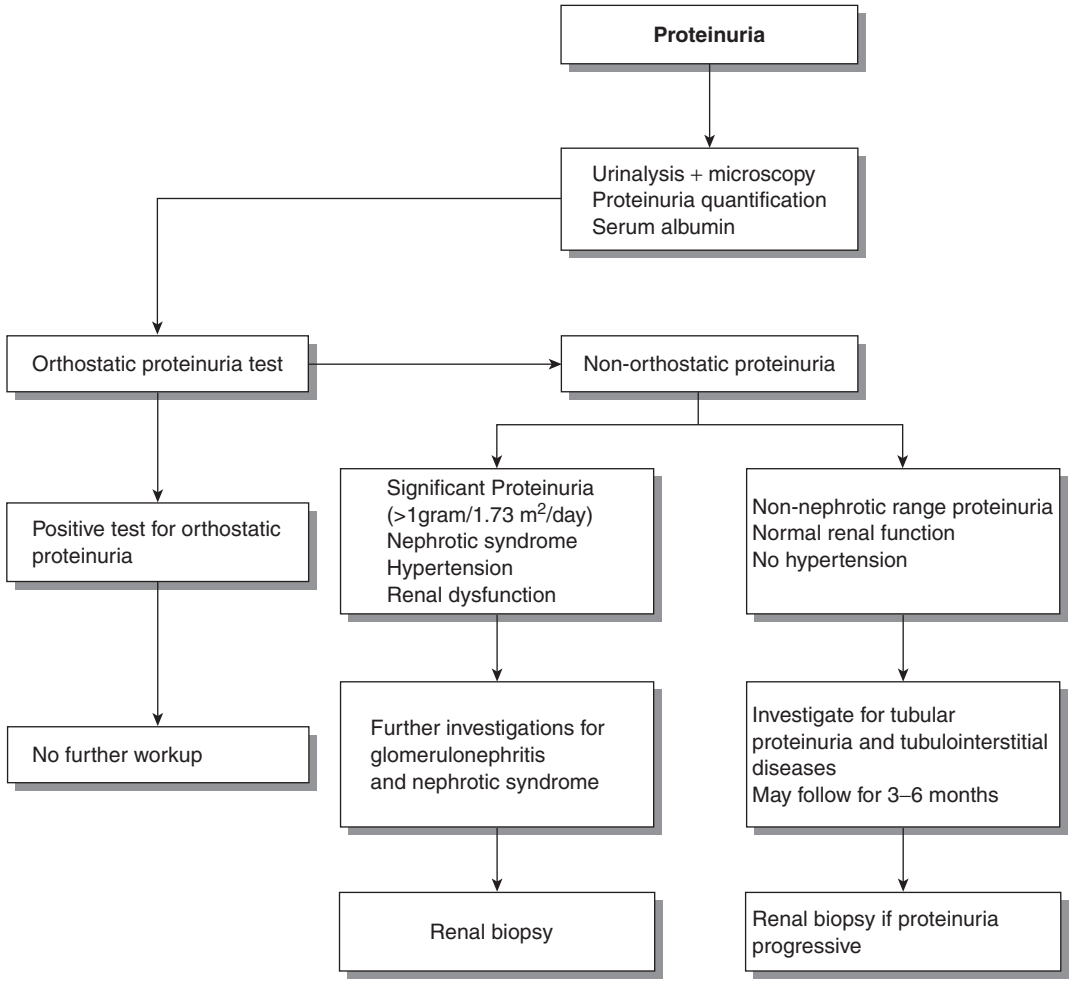

Figure 9.7 Algorithm for evaluation of proteinuria.

obtain differential timed urine collections of 12 hours each – while the patient is resting and in the upright posture. Protein is estimated in each of these urine collections. The diagnosis of orthostatic proteinuria is established by documenting normal (calculated 24-hour) urine protein excretion in the recumbent sample, while the upright sample has significant proteinuria.

Alternately, a spot urine collection is obtained after 8–10 hours of flat overnight rest (first morning void after waking up), and another sample is requested later in the day after 4–6 hours of ambulation. It is important to remind the patients to empty their bladder prior to sleeping. Both samples of urine are then evaluated for protein/creatinine ratio. Normal urinary protein/creatinine ratio in the first morning sample (<0.2), coupled with an abnormal protein/creatinine ratio in the afternoon sample, is suggestive of orthostatic proteinuria.

Prognosis

Orthostatic proteinuria is considered to have a benign prognosis.[50,51] Rytand and Spreiter followed 6 patients with orthostatic proteinuria originally diagnosed by Thomas Addis.[50] After 50 years of follow up, none of them had evidence of renal disease or worsening of their proteinuria.

Microalbuminuria

Microalbuminuria is defined as urinary excretion of albumin above normal values, but less than that detected by a traditional dipstick.[52] A persistent elevation of urinary albumin excretion of 30–300 mg/day (20–200 μg/min) is quantitatively considered as microalbuminuria.[53] Although persistent microalbuminuria is well known to be a harbinger of renal morbidity in patients with diabetes mellitus or hypertension,[54] microalbuminuria has also been shown to be a predictor of early glomerular injury in children with sickle cell disease, correlating with increasing age and lower hemoglobin levels.[55,56] While a 24-hour collection of urine is considered the 'gold standard' for assessing microalbuminuria, quantitation of microalbuminuria/urinary creatinine in a random spot urine collection (U_{MA}/U_{Cr}) has been shown to be comparable to a 24-hour urine collection.[57–59] A normal U_{MA}/U_{Cr} is <30 mg/g creatinine, and a value between 30 and 299 mg/g creatinine is suggestive of microalbuminuria.[60]

The American Diabetes Association (ADA) recommends microalbumin/creatinine ratio as the preferred method for evaluating microalbuminuria in diabetic patients.[61] This screening may also be performed by a 24-hour urine collection, or a timed collection of less than 24 hours. The ADA and the American Kidney Foundation recommend screening type 1 diabetics for microalbuminuria after 5 years of disease, type 2 diabetics at the time of diagnosis, and both groups annually thereafter.[61]

Screening for renal disease

The American Academy of Pediatrics (AAP) has not recommended routine screening urinalysis, except as part of the physical examination at age 5 years and then once during adolescence (between 11 and 21 years).[62] However, in Asia, several countries perform mass screenings of schoolchildren annually and claim to have seen an impact on the incidence of end-stage renal disease (ESRD).[63,64] The cost-effectiveness of such programs has been questioned, however.[63] Despite the increasing incidence of CKD in the United States, an analysis of screening adults for proteinuria did not find the tests to be cost-effective.[65] There was improvement in the cost-effectiveness ratio, provided the screening was selectively directed toward high-risk groups or conducted at 10-year intervals. A similar analysis in children also concluded that multiple screening dipstick urinalysis in asymptomatic patients was not cost-effective.[66] Therefore, the AAP guidelines appear to be reasonable, although a modified screening schedule in patients with a known family history of CKD should be considered.

Proteinuria and progression of renal disease

Because of direct correlation of urinary protein level with progression to CKD,[67–69] proteinuria has traditionally been considered to be a consequence of progressive renal injury and a *marker* of the severity of renal disease. However, there has been a paradigm shift in recent years, to think of urinary protein as a contributory *cause* of renal disease progression.[70,71] Experimental evidence suggests that urinary proteins may elicit proinflammatory and profibrotic effects that play a role in tubulointerstitial damage. Several potential mechanisms of proteinuria-induced tubule cell injury have been proposed. First, is the concept of 'misdirected' filtration, which proposes that podocyte injury causes adhesion of the glomerular tuft to Bowman capsule, and accumulation of the filtrate outside of Bowman space and into the periglomerular space, ultimately leading to glomerulosclerosis.[72,73] Another proposed mechanism is luminal obstruction by protein casts.[74] Finally, excessive protein uptake by the proximal tubular cells in proteinuric states may lead to focal extravasation of cell contents into the neighboring interstitium, followed by an inflammatory reaction and tubulointerstitial fibrosis.[75,76] It is largely unclear whether proteinuria is simply the result of, or a culprit in, progressive renal disease. However, it is generally felt that an inverse relationship between level of proteinuria and long-term renal survival validates an aggressive use of antiproteinuric therapies.[70,71,77–79] The possible role of proteinuria in causing progressive renal injury also raises a cautionary flag regarding overzealous intravenous albumin infusions in the treatment of nephrotic edema.[70,80]

Concluding remarks

The evaluation of hematuria and proteinuria in children requires a directed approach based on history and physical findings. Every child does not require the whole battery of potential tests. Recent data show that intervention in cases of significant fixed proteinuria is warranted, and that perhaps some caution ought to be exercised in aggressive administration of intravenous proteins.

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Part III

Parenchymal diseases

10 Acute glomerulonephritis and rapidly progressive glomerulonephritis

V Matti Vehaskari and Diego H Aviles

A child manifesting acute onset of kidney disease, or with rapidly deteriorating kidney function, is often a diagnostic challenge. Management of these patients involves establishing diagnosis, need for a renal biopsy, and consideration for urgent dialysis and other medical therapies. Both acute postinfectious glomerulonephritis and rapidly progressive glomerulonephritis can present with a rapid clinical onset. It is also important to note that chronic glomerulonephritides, such as systemic lupus erythematosus (SLE) nephritis or membranoproliferative glomerulonephritis (MPGN), may manifest an acute onset and need to be considered in the diagnostic evaluation of patients with acute nephritis.

Acute postinfectious glomerulonephritis

Epidemiology

Acute postinfectious glomerulonephritis (AGN) may occur at any age, but it is more commonly encountered between the ages of 2 and 15 years.[1–4] Most studies report a male preponderance.[3,4] Geographical variations in the incidence of AGN are well known. With improving living standards, the incidence has decreased in most Western countries over the past half century,[1,5,6] but AGN is still a major health concern in many geographic regions of the world.[3,6,7]

Because AGN follows upper respiratory or skin infection with group A β-hemolytic streptococcus in over 90% of cases, the term 'acute poststreptococcal glomerulonephritis' (APSGN) is often used synonymously with AGN. APSGN associated with pharyngotonsillitis is more common in temperate climates, especially during winter, while impetigo-associated disease is more common in warm and humid climates during summer.[8,9] Epidemic outbreaks of APSGN may occur under crowded and poor sanitary conditions.[1,4,10,11] Studies during epidemics have shown that cases with asymptomatic disease outnumber those with overt nephritis.[10,12] In some populations, scabies-associated streptococcal skin infections are responsible for a large proportion of APSGN.[1] The overall risk of developing APSGN after a streptococcal infection is probably less than 2%, but the risk rises to 5–25% if the infecting streptococcal strain is known to be nephritogenic.[10,12]

Although much less common, AGN may result from a variety of other bacterial and viral infections, such as staphylococci, pneumococci, *Yersinia*, *Mycoplasma pneumoniae*, influenza virus, adenovirus, coxsackie virus, cytomegalovirus, Epstein–Barr virus, varicella virus, mumps virus, measles virus, and parvovirus B19 (Table 10.1).[13–15] Rarely, AGN can occur with chronic bacterial infections, such as subacute endocarditis, ventriculoatrial shunt infections, and deep-seated abscesses.[13,16]

Clinical presentation

The onset of APSGN typically occurs 7–14 days after an upper respiratory tract infection, and as long as 6 weeks after impetigo. The primary infection may remain undetected in some cases. The presentation of AGN varies according to disease severity. A typical presentation is the combination of oliguria, hypertension, mild lower extremity or periorbital edema, hematuria, and proteinuria, with a modest impairment of renal function. Pulmonary edema due to fluid overload may be present in moderately severe cases (Figure 10.1). Gross hematuria with brownish (coke-or-tea-colored) discoloration of urine is present

Table 10.1 Conditions that present as acute nephritic syndrome

1. Acute postinfectious glomerulonephritis
   Bacterial infections:
   - Poststreptococcal glomerulonephritis
   - Staphylococci
   - Pneumococci
   - *Yersinia*
   - *Mycoplasma pneumoniae*

   Viral infections:
   - Influenza virus
   - Adenovirus
   - Coxsackie virus
   - Cytomegalovirus
   - Epstein–Barr virus
   - Varicella virus
   - Mumps virus
   - Measles virus
   - Parvovirus B19
2. Membranoproliferative glomerulonephritis
3. IgA nephropathy
4. Henoch–Schönlein purpura nephritis
5. Systemic lupus erythematosus nephritis
6. Vasculitis
   - Microscopic polyangitis
   - Wegener's granulomatosis
   - Churg–Strauss syndrome
7. Rapidly progressive glomerulonephritis

in up to 50% of the patients. Significant leukocyturia may be seen in some patients with AGN. Dull abdominal or flank pain and malaise may be present. Severe hypertension and hypertensive encephalopathy, manifesting as headache or even seizures, may be the initial presenting symptoms in a rare patient. Less severe cases manifest microscopic or gross hematuria without edema, hypertension, proteinuria, or decreased kidney function. Nephrotic syndrome and acute renal failure are uncommon, but may occur.

Pathology

Light microscopy in the acute phase of APSGN shows diffuse endocapillary cell proliferation, swelling, and narrowing of glomerular capillary lumens (Figure 10.2A). Infiltration of the glomeruli with neutrophils and monocytes is a common finding. The hallmark of APSGN is the electron microscopy findings of large subepithelial deposits ('humps'), believed to be immune complexes (Figure 10.2B). Immunofluorescence microscopy reveals coarsely granular staining of the capillary loops for IgG and complement C3.[13] The presence of IgM and IgA is variable. After the acute phase, mesangial hypercellularity with positive immunofluorescence may persist for months to years, despite clinical recovery.[2,17] In non-streptococcal AGN, the renal pathology is more variable and may include subendothelial deposits in addition to mesangial and endothelial cell proliferation.[13–15]

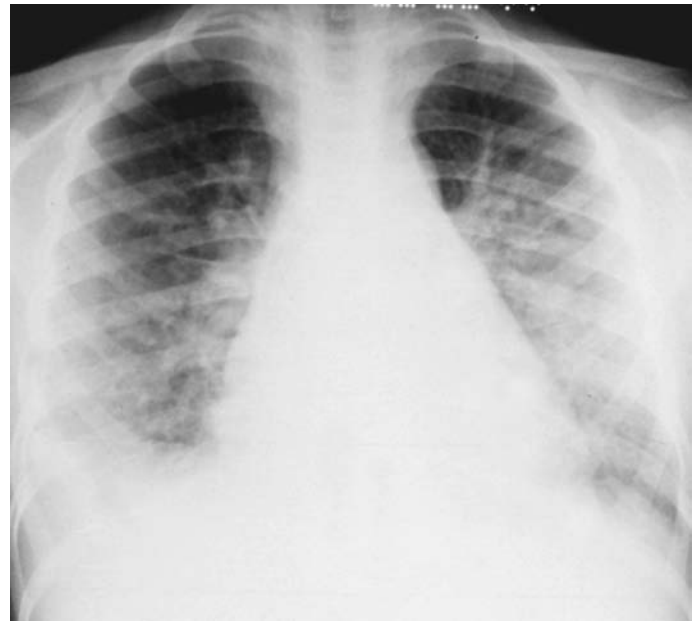

Figure 10.1 Chest X-ray of a patient with poststreptococcal glomerulonephritis showing pulmonary edema.

Pathogenesis

AGN is believed to result from the host immune response to the preceding infection. Only a few streptococcal serotypes are capable of causing APSGN. M serotypes 1, 2, 3, 4, 12, 18, 25, and 49 are most commonly seen with pharyngitis-associated ASPGN, whereas types 2, 49, 55, 57, and 60 are seen commonly with skin infection-associated ASPGN.[18] Glomerular immune complexes may represent 'trapped' circulating antigen–antibody complexes, or immune complexes formed in situ within the glomerular capillary wall.[19–23] In-situ immune complex formation may be initiated by antibodies cross-reacting with glomerular capillary wall components,[19] or by circulating microbial antigens with affinity for the capillary wall, such as streptococcal M protein or endolysin.[20,23–25] Once formed, the immune complexes activate complement, cytokines, and other mediators of glomerular injury.[26]

Rapidly progressive glomerulonephritis

Definition

Rapidly progressive glomerulonephritis (RPGN), or crescentic glomerulonephritis, is a clinicopathologic condition that is characterized by a rapid deterioration of renal function and demonstration of 'crescents' affecting at least 50% of the glomeruli in an adequate biopsy specimen.[27,28] However, the definition is arbitrary and patients with lesser degrees of crescent formation may progress into full-blown RPGN. Crescents form in the Bowman space surrounding the glomerular capillary tuft,

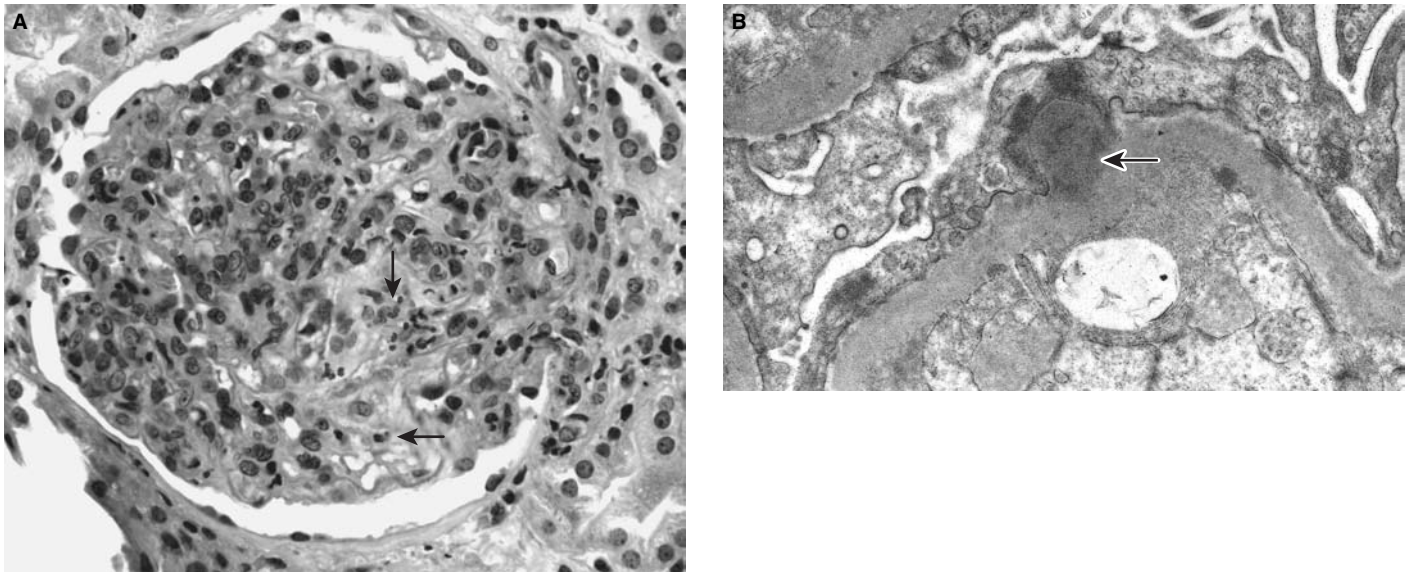

Figure 10.2 Acute postinfectious glomerulonephritis. (A) Light micrograph showing a glomerulus in a patient with acute poststreptococcal glomerulonephritis. Glomerular capillaries are obliterated in many areas due to endothelial cell swelling. Numerous neutrophils (arrows) are noted in the glomerulus. (B) Electron micrograph showing a large subepithelial deposit or 'hump' (arrow) in a patient with poststreptococcal glomerulonephritis. (Both photographs courtesy of Dr. Randall Craver, Louisiana State University.)

and are initially composed of infiltrating macrophages and proliferating glomerular epithelial cells. Later, these organize into fibroepithelial crescents, and eventually into fibrotic crescents. Severely affected glomeruli may eventually progress to global sclerosis (Figure 10.3).

Epidemiology

RPGN is an uncommon disorder in children and its precise incidence is unknown. Although adolescents are affected more commonly,[29–32] RPGN may occur in younger children, including infants.[29,33] Since severe APSGN may lead to RPGN, increased incidence of RPGN may be observed during large epidemics of streptococcal infection.[32,34] A few familial cases of RPGN have been reported.[35]

Classification

RPGN is not a single disease entity. Rather, the crescents are believed to be the result of severe non-specific glomerular injury, with numerous underlying causes. Current classification of RPGN is based on the nature of immune deposits seen in the renal biopsy. It is categorized as:

- immune complex-mediated
- anti-glomerular basement membrane (anti-GBM) antibody-mediated or
- pauci-immune.[28]

The distribution of these subtypes in children differs from that in adults (Table 10.2).

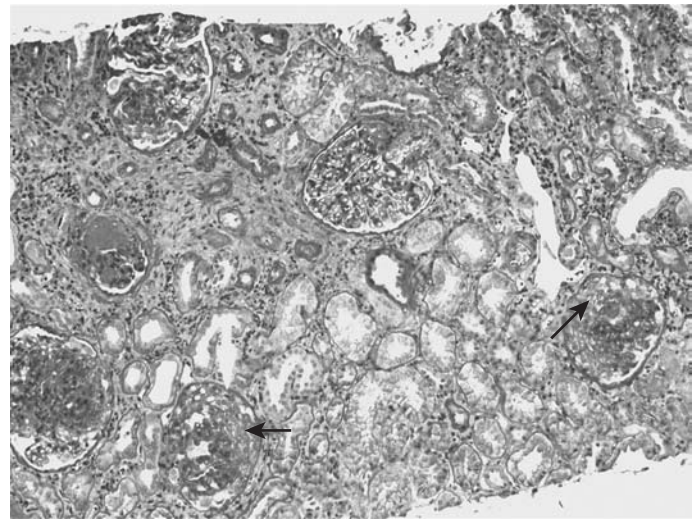

Figure 10.3 Light microscopy in a patient with crescentic glomerulonephritis. The arrows point to fibrocellular crescents. (Photograph courtesy of Dr. Randall Craver, Louisiana State University.)

Immune complex-mediated RPGN

In a large series from the United States, immune complex-mediated RPGN accounted for 45% of all RPGN in children less than 20 years of age, in contrast to 35% in the 21–60-year group, and only 6% in patients over 60.[36] Also, geographical variations in the distribution have been reported. Renal biopsy in immune complex-mediated RPGN is characterized by the presence of glomerular immune complexes, that can be documented by immunofluorescence and electron microscopy. The

Table 10.2 Rapidly progressive glomerulonephritis (RPGN): distribution of subtypes in children and in adults

	Age 1–20 years (73 patients)	All ages (632 patients)
Immune complex-mediated RPGN	45%	24%
Pauci-immune RPGN	42%	60%
Anti-GBM antibody-mediated RPGN	12%	15%
Other	0	1%

Modified and reproduced with permission from Jennetle JC[36]

localization of the immune complexes within the glomeruli is dependent on the underlying etiology. Most pediatric cases of immune complex-mediated RPGN are associated with chronic glomerulonephritides, such as MPGN, IgA nephropathy, Henoch–Schönlein purpura nephritis and SLE nephritis, or with APSGN.

Anti-glomerular basement membrane antibody-mediated RPGN

Anti-glomerular basement membrane (anti-GBM) antibody-mediated RPGN is the most aggressive form of RPGN, and accounts for approximately 12% of pediatric cases.[36] The disease is mediated by binding of circulating autoantibodies to the glomerular basement membrane. Immunofluorescence microscopy reveals linear deposits of IgG, with or without accompanying C3 along the capillary loops. Anti-GBM antibody cross-reacts with pulmonary basement membrane, resulting in pulmonary injury and pulmonary hemorrhage, this condition being known as Goodpasture syndrome. Isolated renal disease without pulmonary manifestations is present in approximately 50% of the cases.[36–38]

Pauci-immune RPGN

Pauci-immune RPGN is the second most common type of RPGN in children (see Table 10.2). The diagnosis is made by demonstration of extensive glomerular crescent formation without evidence of immune complex or anti-GBM antibody deposition. Pauci-immune RPGN is often associated with systemic small-vessel vasculitis, such as Wegener's granulomatosis (WG), microscopic polyangiitis, and Churg–Strauss syndrome. In a minority of cases, the disease is limited to the kidney.

Approximately 80% of patients with pauci-immune RPGN have circulating antineutrophil cytoplasmic antibodies (ANCA).[36,39] In WG, ANCA are directed against proteinase 3 (PR3) and give a cytoplasmic staining pattern in neutrophils (c-ANCA). Perinuclear staining (p-ANCA) correlates with anti-myeloperoxidase antibodies and is typical of the other, non-WG forms of pauci-immune RPGN, although p-ANCA may be seen in a minority of patients with WG.[40] Atypical ANCA staining patterns due to other antibodies are occasionally present.[41] It is now believed that ANCA plays a role in the pathogenesis of RPGN by participating in neutrophil activation that ultimately results in endothelial damage.[40,42–44] The primary causes of ANCA formation, however, remain unclear. Anti-GBM antibodies and ANCA may coexist in some patients.[45] Rarely, drugs, such as propylthiouracil and hydralazine may induce ANCA-positive RPGN.[39,46–48]

Clinical manifestations

The manifestations of RPGN can vary from asymptomatic proteinuria and hematuria, or increased serum creatinine, to life-threatening renal failure or hypertensive crisis. Nephritic features such as hypertension, oliguria, hematuria, or nephrotic syndrome are also frequently present. Renal failure, requiring dialysis, may be present at the time of initial diagnosis, or develop subsequently over days to weeks. A more protracted course is also seen at times. Even in asymptomatic cases, progressive renal disease and declining kidney function is common.

If RPGN is associated with systemic disease, extrarenal symptoms may dominate at presentation, and may precede the onset of renal disease. The organ systems commonly involved in systemic disease-associated RPGN are listed in Table 10.3. In SLE and Henoch–Schönlein purpura-associated RPGN, manifestations of systemic disease are often seen in conjunction with RPGN. In ANCA-positive RPGN, such as WG, systemic manifestations may lag behind the first signs of renal disease. Pulmonary hemorrhage, a life-threatening complication, may accompany RPGN, especially those associated with systemic disorders. Chronic upper and lower respiratory tract disease consisting of chronic sinusitis and ear infections, hearing loss, oral or nasal ulcers and inflammation, nasal septal perforation or nasal bridge collapse, and pulmonary nodules or cavitation is characteristically seen in WG. Granulomas in the respiratory tract are present in the areas of the affected portions of the respiratory tract. Musculoskeletal symptoms, especially arthralgias, are common in all forms of ANCA-positive RPGN. Cutaneous nodules and other skin involvement may occur in WG and Churg–Strauss syndrome. Eosinophilic gastroenteritis frequently accompanies the acute phase of Churg–Strauss syndrome.

Diagnostic evaluation

Investigations of nephritic syndrome (oliguria, edema, hypertension, proteinuria, and hematuria) should be initiated towards ruling out the possibility of APSGN and whether or not the patient has RPGN. A renal biopsy will be necessary in

Table 10.3 Differential diagnosis of acute nephritic syndrome

	APSGN	MPGN	IgA-GN	SLE	HSP	aGBM	RLV	WG	MPA	C-S
Symptoms										
Constitutional	+/–			+	+/–	+		+	+	+
Gastrointestinal					+					+/–
Pulmonary						+		+	+	+
Upper respiratory								+		
Joint				+	+			+/–	+/–	+
Skin				+	+			+/–	+/–	+/–
Laboratory										
Low C3	+	+		+						
ASO/Streptoz.	+									
ANA				+						
a-GBM ab						+		+/–	+/–	
c-ANCA								+		
p-ANCA							+		+	+
Eosinophilia								+/–		+

+ denotes observed in most patients; +/–, denotes observed in less than 50% of patients.
APSGN, acute postinfectious glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; IgA-GN, immunoglobulin A nephropathy; SLE, systemic lupus erythematosus nephritis; HSP, Henoch–Schönlein purpura nephritis; aGBM, anti-glomerular basement membrane antibody-mediated glomerulonephritis; RLV, renal-limited vasculitis; WG, Wegener's granulomatosis; MPA, microscopic polyangiitis; C-S, Churg–Strauss syndrome; C3, complement C3; ASO, antistreptolysin O antibody; Streptoz., streptozyme test; ANA, antinuclear antibody; c-ANCA, cytoplasmic staining with antineutrophil cytoplasmic antibody; p-ANCA, perinuclear staining with antineutrophil cytoplasmic antibody.

order to ascertain the diagnosis of RPGN. Follow-up investigations are needed to determine any underlying systemic disorder that may accompany renal disease, so that appropriate therapy can be advocated for the patient.

Historical data

Streptococcal pharyngitis precedes development of gross hematuria and other symptoms of APSGN by 2–4 weeks. Acute nephritic syndrome, including gross hematuria, may also be a manifestation of IgA nephropathy. However, gross hematuria in IgA nephropathy occurs within 24–48 hours of onset of upper respiratory tract infection, and is often referred to as 'synpharyngitic hematuria'.

In temperate climates, history of recent skin infection should also be ascertained. Symptoms of systemic disorders such as fever, joint pains, purpuric rash, and malar rash, symptoms of sinusitis, cough, and pulmonary symptoms, should be documented.

Throat culture

Throat culture for group A β-hemolytic streptococcal infection should be obtained, even though positive findings may not be always be present by the time of the patient's presentation.

Streptococcal antibody titers

A positive streptococcal antibody titer is considered evidence supportive of recent streptococcal infection, but does not confirm the existence of glomerulonephritis. Streptozyme panel, which includes antibodies against four streptococcal antigens, is a more sensitive test than the commonly used antistreptolysin O (ASO) titer. In APSGN resulting from skin infection, the anti-DNase B antibody titer (included in streptozyme panel) may be positive in the absence of the ASO titer being significantly elevated.[49] In AGN due to non-streptococcal infections, specific antibody titers should be obtained when warranted by clinical suspicion.

Complement studies

Low C3 complement is central in the diagnosis of APSGN. In some cases of APSGN, C3 complement returns to a normal level in less than 2 weeks, whereas C3 complement returns to normal by 8 weeks in all cases with this disorder.[50–52] Persistence of low complement C3 beyond 8 weeks should indicate a diagnosis other than APSGN. It is important to recognize that approximately 15% of patients with APSGN do not demonstrate a low C3 level,[50] perhaps reflecting a transient complement utilization and recovery in these patients. Apart from APSGN, low complement C3 is also be seen in SLE and in MPGN (see Table 10.3). Complement C4 level is usually normal in APSGN, but can be slightly decreased in some cases.[50,52]

Directed evaluation

If the initial clinical and laboratory assessment in a patient with nephritic syndrome does not support the diagnosis of APSGN, further evaluation for other types of glomerulonephritis, especially RPGN, should be pursued (Table 10.4). Signs of systemic disease should be looked for (see Table 10.3).

Table 10.4 Evaluation of acute nephritic syndrome

Initial evaluation
Blood count (rule out HUS)
BUN, creatinine, electrolytes, serum albumin
Quantify proteinuria (urine protein:creatinine ratio)
Culture of throat and skin lesions
Streptococcal antibody titers (ASO, anti DNase B, antihyaluronidase)
Complement C3, C4
Further evaluation
(If the diagnosis of APSGN is ruled out)
Monitor BUN, creatinine, electrolytes
Hepatitis B panel, hepatitis C titer
ANA (full lupus panel if ANA positive)
ANCA
Anti-GBM antibody titer (if pulmonary involvement)
Renal biopsy

HUS, hemolytic-uremic syndrome; BUN, blood urea nitrogen; ANA, antinuclear antibody; SLE, systemic lupus erythematosus; APSGN, acute postinfectious glomerulonephritis; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

Anti-nuclear antibody
The antinuclear antibody (ANA) test has a high negative predictive value for SLE, but low-level false-positive titers are common. A positive ANA test should be pursued with further antibody diagnostic tests for SLE.

ANCA
ANCA titers may be helpful, but negative titers do not rule out RPGN. A positive titer for c-ANCA is suggestive of WG and positive p-ANCA may be indicative of pauci-immune RPGN. An ANCA titer can be utilized as a test for measuring the clinical course during follow-up and therapy.

Anti-GBM antibody
In patients with suspected Goodpasture's syndrome, an anti-GBM antibody assay can provide an objective measure that can be followed during therapy.

Renal biopsy
When RPGN is suspected, arriving at a histologic diagnosis is necessary in order to guide therapy. Therefore, if severe renal failure or rapidly rising serum creatinine is noted, and the diagnosis remains uncertain, a renal biopsy should undertaken.

Pulmonary disease evaluation
If Wegener's granulomatosis is suspected in a patient with RPGN, examination of the nose and sinuses, as well as a CAT scan to evaluate the sinuses should be conducted for evidence of granuloma. Radiologic examination of the chest should also be undertaken in suspected cases of WG and Goodpasture's syndrome.

Management

Acute postinfectious glomerulonephritis

The treatment of AGN consists of supportive therapy only. Children without volume expansion, hypertension, electrolyte problems, or decreased kidney function need only close follow-up. Patients who develop significant renal impairment or hyperkalemia generally require hospitalization for monitoring and appropriate fluid and electrolyte management.

Antibiotics
Antibiotic treatment after the onset of APSGN does not alter the course of the disease. Antibiotic prophylaxis given to family members may reduce the risk of spread of APSGN.[1,4,53]

Fluid overload and hypertension
When present, hypertension is the result of sodium retention and volume expansion. Therefore, treatment is directed at sodium restriction and diuretic therapy, in addition to antihypertensive medication, if necessary. The combination of a loop or thiazide diuretic with a calcium channel blocker is usually effective. Caution should be exercised with the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers because of the risk of hyperkalemia or renal failure.

Hyperkalemia
Potassium intake should be restricted. If serum potassium is rising, potassium exchange resin, sodium polystyrene sulfonate (Kayexalate), can be administered orally. Life-threatening hyperkalemia should be treated as an emergency using intravenous bicarbonate, glucose, and insulin, or calcium gluconate, as appropriate. Rare cases of severe or symptomatic hyperkalemia should be treated with dialysis.

Dialysis
Hemodialysis or continuous venovenous hemofiltration may be necessary in severe cases with uremia, especially if diuretic-unresponsive anuria or oliguria is present.

Rapidly progressive glomerulonephritis

Early prompt and effective treatment of RPGN is necessary for bringing the disease into remission. Recovery of renal function can occur even in patients on prolonged dialysis.[54] Because of limited data in children,[55–58] current therapeutic recommendations are mostly derived from adult experience.[39,59–65]

The standard treatment of RPGN consists of glucocorticoids and cytotoxic drugs. Because patients with only mild renal impairment and lesser percentage of crescentic glomeruli, or patients with RPGN due to AGN, tend to do better, their immunosuppressive regimen may not need to be as intense as that of more severely affected cases of RPGN.[36]

Glucocorticoids

Treatment of RPGN is usually initiated with intravenous methylprednisolone 'pulses' (10 mg/kg/day) for 7–10 days, followed by high-dose oral steroids (1–2 mg/kg/day, up to a maximum of 80 mg/day). The steroid dose is gradually tapered over several months to a year, based on the patient's clinical response. Low maintenance therapy with steroids may be considered in the most severe cases, depending on clinical response and the disease activity. In other cases, steroids are eventually discontinued once an improvement in the disease activity is achieved.

Cytotoxic therapies

Early oral or intravenous cyclophosphamide treatment is recommended for all forms of RPGN. Many centers prefer the intravenous route for cyclophosphamide administration, but its superiority to oral therapy has not been convincingly demonstrated. The argument for intravenous cyclophosphamide is a lower cumulative dose of the drug, compared with oral therapy.

When used as intravenous therapy, cyclophosphamide is given monthly in a dose of 500–1000 mg/m^2 for 3–6 months. A dose of 2 mg/kg/day is commonly used for oral therapy. Drug-induced neutropenia may be a dose-limiting factor and must be monitored. The frequency of other side effects, including interstitial cystitis, may be lower with the intravenous route of administration. The combination of high-dose steroids and cyclophosphamide is effective in inducing remission in up to 90% of adult patients with RPGN.

Because of the high rate of complications associated with long-term cyclophosphamide treatment, switching to maintenance therapy with azathioprine or methotrexate has been advocated once the disease is in clinical remission.[63,66] The optimal length of azathioprine or methotrexate treatment has not been defined, but discontinuation of the therapy should be considered after a patient has been in remission for 1 year.[40] Mycophenolate mofetil (CellCept), a newer cytotoxic agent, may be useful in maintenance therapy of patients with RPGN. However, no data are available yet for efficacy of this therapy in the treatment of RPGN.

ANCA titer may be useful in following disease activity and as a guide to therapy.[59] The relapse rate of RPGN on maintenance therapy is high, with up to 50% or more requiring re-institution of aggressive treatment.

Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) may be beneficial as an adjuvant therapy in the acute phase, but its role remains poorly defined because of a lack of large controlled studies. Its use has been advocated especially in Goodpasture's syndrome and in ANCA-positive RPGN that is accompanied by pulmonary hemorrhage.[36,67,68]

Other therapies

Other potential treatments include calcineurin inhibitors (cyclosporine or tacrolimus), leflunomide, deoxyspergualin, and intravenous immunoglobulin, but the role of these agents in the therapeutic regimen is not established.[36,40,59] More recently, limited uncontrolled reports have suggested that treatment with antibodies against B or T cells, or with tumor necrosis factor-α antagonists, in addition to conventional treatment, may benefit some patients.[69–73]

Clinical course and prognosis

Acute postinfectious glomerulonephritis

Despite some earlier reports to the contrary, the overwhelming majority of children with APSGN are believed to make a full recovery without significant long-term consequences.[1,74–78] Recurrences of APSGN are rare.[79] Progression to chronic kidney disease (CKD) and end-stage renal disease (ESRD) may occur in exceptionally severe cases of APSGN.[80,81] Despite lack of long-term follow-up data in children, AGN due to other infectious agents (non-streptococcal) is generally considered to have a favorable prognosis.

Follow-up of AGN is important to document full recovery. Proteinuria associated with APSGN usually resolves by 6–8 weeks. Prolonged proteinuria for more than 3 months may indicate irreversible renal injury, and should be viewed with concern. Gross hematuria usually improves within 1–3 weeks but microscopic hematuria can persist for up to 1 year and is not an indicator of poor prognosis. Recovery of serum complement C3 to normal usually takes 6–8 weeks.[50] Persistent hypocomplementemia beyond 8 weeks requires a careful search for other diagnoses, such as MPGN and SLE nephritis.

Rapidly progressive glomerulonephritis

Untreated non-immune complex RPGN carries a high risk for ESRD, and mortality can be as high as 80%.[59,82] With treatment, remission of RPGN can be achieved in most patients, but the relapses occur in 30–50% patients.[54,59,63,83] Prognosis of immune complex-associated RPGN is somewhat better, especially in children.[36,56] Indicators of poor renal prognosis are impaired renal function at onset and large percentage fibrous crescents on renal biopsy.[36]

Heavy immunosuppressive regimens used for treatment of RPGN introduce risks of their own for acute life-threatening infections and concern for long-term complications, including infertility and malignancies.[82,84]

Case history

A 10-year-old boy was admitted with complaints of facial puffiness and decreased urine output for four days. He denied having any other systemic symptoms or taking any medications during the past several months. Physical examination was significant for hypertension (150/102 mmHg), and 2+pretibial pitting edema. There was no evidence of any facial rash or petechia on the skin. Hemoglobin 11.8 mg/dl, electrolytes normal, serum

albumin 3.0 mg/dl, blood urea nitrogen (BUN) 60 mg/dl, serum creatinine 2.0 mg/dl, and urinalysis demonstrated large blood and 3+ (300 mg/dl) proteinuria. Two days after admission, his serum creatinine rose to 4.5 mg/dl and BUN was 95 mg/dl. The ASO titer was positive (1400 U/ml), and serum complement C3 level was normal.

Comment

The apparent short duration of the illness pointed towards an acute disease, such as AGN (despite normal C3) or RPGN, but exacerbation of undiagnosed chronic disease could not be ruled out. Absence of signs of systemic disease made generalized vasculitis less likely. Rapidly declining kidney function raised the concern of RPGN, and a renal biopsy was performed. Renal biopsy showed cellular crescents affecting 17 of 25 glomeruli (68%). Immunofluorescence microscopy was negative for any immune deposits or linear staining of the GBM. The ANCA titer sent on admission was positive for p-ANCA. Based on these renal biopsy findings, the patient was diagnosed as having renal-limited pauci-immune RPGN.

Because the patient's crescents were cellular, he may have had a good chance of responding to therapy. Treatment was begun with intravenous methylprednisolone pulses, 20 mg/kg on alternate days for six doses. Thereafter, oral prednisone was begun at 2 mg/kg/day, recommended for 1 year, and would be tapered slowly. Monthly intravenous cyclophosphamide infusions at a dose of 500 mg/m^2/dose was initiated and continued for 6 months.

At 6 months of follow-up, his serum creatinine was 1.5 mg/dl, BUN 25 mg/dl, urine protein/creatinine ratio 0.7 mg/mg, and the ANCA titer was negative. The patient was considered to be in remission of RPGN, with residual renal damage. Maintenance therapy with azathioprine (2 mg/kg/day) was recommended for 12 months while tapering him off prednisone. Renal function, urinary protein excretion, and ANCA titers were monitored monthly for any evidence of relapse of the disease.

Concluding remarks

Despite a decrease in incidence, AGN is still one of the most common kidney diseases in children. The disease is relatively benign in most children. Whereas prevention is possible by antibiotic prophylaxis, improving overcrowding and poor living conditions can reduce the burden of the disease worldwide.

RPGN is uncommon in children. Because prompt treatment is essential, a high index of suspicion is necessary, and renal biopsy should be considered early in patients with declining kidney function. The current empirical treatment of RPGN is unsatisfactory, and the relapse rate is unacceptably high. Replacing the non-specific broad-based immunosuppressive treatment with targeted therapy with greater efficacy and fewer side effects should be the future goal. Ideally, the therapy should be based on better understanding of the pathophysiology of each type of RPGN. The use of specific antibodies is a step in that direction, but truly tailored antibody treatment will require better delineation of the immune and non-immune mechanisms involved in each subtype of RPGN.

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11 Nephrotic syndrome

Rudolph P Valentini and William E Smoyer

Nephrotic syndrome is among the most common types of kidney diseases seen in children. It is characterized by massive proteinuria, hypoalbuminemia, and edema, although additional clinical features such as hyperlipidemia are usually also present. Children with this condition often present with sudden development of periorbital swelling, with or without generalized edema. Although nephrotic syndrome most often occurs as a primary disorder in children, it can also be associated with a variety of systemic illnesses. Structural and functional abnormalities in the glomerular filtration barrier resulting in severe proteinuria are responsible for the clinical manifestations of nephrotic syndrome.

Historical perspective

Historically, both edema and proteinuria have been clinically recognized for over 2000 years. Roelans has been credited with the clinical description of children with nephrotic syndrome in 1484, and Zuinger described its clinical deterioration to chronic renal failure.[1] The term 'nephrotic syndrome', however, was coined by Henry Christian in 1929.[2] Prior to the introduction of antibiotics and immunosuppressive therapies for nephrotic syndrome, it was well recognized that many patients died of their disease, in some cases the edema would remit spontaneously, or could even be cured.[2] In the 1700–1800s, treatments included such approaches as the induction of malaria or measles, as well as the administration of mercury-containing compounds.

The mortality rate for children with nephrotic syndrome in the pre-corticosteroid era was high (67%).[3] In 1939 the mortality rate first dropped significantly to 42% after the introduction of sulfonamides, and then again to 35% following the introduction of penicillin in 1944.[3] Use of adrenocorticotropic hormone and cortisone in the 1950s resulted in a more profound drop in the mortality rate to 9% in association with dramatic resolution of proteinuria in these patients.[3]

Definitions and clinical classification

Nephrotic syndrome

The diagnosis of nephrotic syndrome requires the presence of edema, severe proteinuria (> 40 mg/m^2/h, or a protein:creatinine ratio > 2.0), hypoalbuminemia (< 2.5 g/dl), and hyperlipidemia.[4,5]

Remission of nephrotic syndrome

Remission represents a marked reduction in proteinuria (to < 4 mg/m^2/h, or urine albumin dipstick of 0 to trace for 3 consecutive days) in association with resolution of edema.[4,5]

Relapse of nephrotic syndrome

Relapse of nephrotic syndrome is defined as recurrence of severe proteinuria (> 40 mg/m^2/h, or urine albumin dipstick ≥ 2+ on 3 successive days), often with a recurrence of edema.[4,5]

Steroid-sensitive nephrotic syndrome

Patients who enter remission in response to corticosteroid treatment alone are referred to as having steroid-responsive or steroid-sensitive nephrotic syndrome (SSNS).

Steroid-resistant nephrotic syndrome

Patients with nephrotic syndrome who fail to develop remission after 8 weeks of corticosteroid treatment are referred to as having steroid-resistant nephrotic syndrome (SRNS).[4,5] It should be noted, however, that significant discrepancies exist in the literature about the definition for SRNS. Whereas some authors define this state as a failure to develop remission after 4 weeks of prednisone at a dose of 60 mg/m^2/day, others define it as failure to develop remission after 4 weeks of prednisone at a dose of 60 mg/m^2/day followed by 4 weeks of alternate-day prednisone at a dose of 40 mg/m^2/dose,[6] or as 4 weeks of prednisone at a dose of 60 mg/m^2/day followed by three intravenous pulses of methylprednisolone at a dose of 1000 mg/1.73 m^2/dose.[6] These discrepancies in definition make a direct comparison of efficacy of therapy for nephrotic syndrome more difficult. The implication of SRNS, however, is that these patients are at significantly higher risk for development of complications of the disease and also for progression to chronic kidney disease (CKD) or end-stage renal disease (ESRD).

Steroid-dependent nephrotic syndrome

Some patients respond to initial steroid treatment by developing complete remission, but develop a relapse either while still receiving steroids, or within 2 weeks of discontinuation of

treatment following a steroid taper. Such patients typically may require continued low-dose treatment with steroids to prevent this rapid development of relapse, and are therefore referred to as having steroid-dependent nephrotic syndrome (SDNS).[7]

Frequently relapsing nephrotic syndrome

If patients develop 4 or more episodes of nephrotic syndrome in any 12-month period, they are referred to as having frequently relapsing nephrotic syndrome (FRNS).[7] Both steroid-dependent and frequently relapsing patients are at increased risk of developing complications of nephrotic syndrome, as well as disease progression to CKD or ESRD. However, these risks are generally considered intermediate between those of steroid-sensitive patients and the significantly increased risks of steroid-resistant patients. In addition, the need for prolonged or more frequent steroid treatment in these patient groups places them at increased risk for steroid-induced side effects when compared with steroid-sensitive patients.

Epidemiology

The annual incidence of nephrotic syndrome has been estimated to range from 2 to 7 new cases per 100 000 children,[4,8–11] and the prevalence is about 16 cases per 100 000 children, or 1 in 6000 children.[4,8] In younger children, boys are about twice as likely to develop nephrotic syndrome as girls, but this imbalance disappears by adolescence such that the incidence in adolescents and adults is equal among males and females.[4,8] The histologic lesion associated with nephrotic syndrome also differs between genders. In a large multicenter study of childhood nephrotic syndrome carried out by the International Study of Kidney Disease in Children (ISKDC), females represented 39.9% of children with minimal change nephrotic syndrome (MCNS) and 30.6% of those with focal segmental glomerulosclerosis (FSGS). In marked contrast, females represented 64.1% of those with membranoproliferative glomerulonephritis (MPGN).[12]

Ethnic differences in nephrotic syndrome are well known. Idiopathic nephrotic syndrome is six times more common among Asian children than in Caucasian children in the United Kingdom, with an incidence of 16 new cases per 100 000 children per year.[13] In contrast, idiopathic nephrotic syndrome is relatively less common among African children, in whom steroid-unresponsive structural glomerular lesions are more common.[14]

In the United States, nephrotic syndrome appears to occur relatively proportionately among children of various ethnic backgrounds. A recent review of nephrotic syndrome from Texas indicated that the distribution of patients closely resembled the ethnic composition of the surrounding community. The racial distribution of the disorder was 49% Caucasian, 20% African-American, and 24% Hispanic.[15]

Race, however, appears to have an important bearing on the histologic lesion associated with nephrotic syndrome. In this same study, the authors found that whereas only 11% of Hispanic and 18% of Caucasian patients with nephrotic syndrome had FSGS, 47% of African-American children had this less-favorable diagnosis.[15] In another study from Kansas City, FSGS was found in 44% of African-American patients and in only 16.7% of Caucasian children.[9] African-American children seem to be at a dramatically increased risk for developing FSGS.

Familial occurrence of idiopathic nephrotic syndrome is also a well-recognized phenomenon and the disorder has been reported in identical twins.[16] In a report of 1877 children with idiopathic nephrotic syndrome in Europe, 3.3% of children were found to have affected family members, most often siblings.[17] The disorder tended to occur in the siblings at the same ages, and with similar biopsy findings and clinical outcomes.[18] At least one locus for SSNS has been mapped to chromosome 1q25, which is near, but distinct from, the NPHS2 gene locus encoding the podocyte protein podocin.[19]

The peak age of presentation of nephrotic syndrome is 2 years, and 70–80% of cases of nephrotic syndrome occur in children less than 6 years of age.[4,8] Age of onset may also be predictive of the underlying histologic lesion causing nephrotic syndrome. MCNS is seen in 80% of children diagnosed with nephrotic syndrome before 6 years of age. In comparison, only 50% of those with FSGS, and 2.6% of those with MPGN present before 6 years.[12] In the same study, the median age at presentation of MCNS was 3 years, compared with 6 years for FSGS, and 10 years for MPGN.[12] These findings suggest that the likelihood of having MCNS decreases with increasing age at onset, whereas the likelihood for having the less-favorable diagnoses of FSGS or MPGN increases.[12,20]

Failure to respond to steroid treatment (SRNS) has an important ramification for the risk of developing progressive renal failure later in life. Within 5 years of diagnosis, 21% of children with FSGS developed ESRD and another 23% developed CKD.[21] Thus, in a child diagnosed as having FSGS, the risk of developing CKD or ESRD within 5 years is almost 50%.

Although the overall prevalence of nephrotic syndrome has remained relatively stable over the last 20 years, a dramatic increase in the incidence of FSGS and decrease in the incidence of MCNS has been reported.[9,15] The reported increased incidence of FSGS needs, however, to be interpreted cautiously, since renal biopsies are generally obtained only in a preselected group of children with atypical presentations, or those exhibiting steroid resistance. It is possible that an increased incidence of FSGS merely represents the fact that a larger percentage of children with SRNS undergo renal biopsies in the present era. This is in marked contrast to an early ISKDC study where all children underwent a renal biopsy at the time of presentation, prior to the institution of treatment.[12] Because renal biopsies are no longer routinely performed in steroid-responsive patients, it is unlikely that the ISKDC observations can be replicated.[22]

Pathogenesis of primary nephrotic syndrome

One of the kidney's most important functions is filtration of the blood by glomeruli, allowing excretion of fluid and waste products, while retaining all blood cells and the majority of blood proteins within the bloodstream. Each glomerulus is composed of numerous capillaries which have evolved to permit ultrafiltration of the fluid that eventually forms urine. The capillary walls are composed of an inner endothelial cell cytoplasm, with pores known as 'fenestrations', the glomerular basement membrane (GBM), and outer glomerular epithelial cells (podocytes) whose distal 'foot' processes are attached to the GBM. Under normal conditions, molecules greater than 42 Å in diameter, or more than 200 kDa, are unable to cross the filtration barrier.[23]

Electrical charge (discussed in Chs 5 and 9) is also an important determining factor for the passage of protein molecules through the glomerular filtration barrier.[24–25] Several reports have indicated a reduction in the negative charge of the GBM in nephrotic syndrome.[26–28] Analysis of size and charge selectivity in 12 children with nephrotic syndrome due to either FSGS or MCNS was, however, unable to demonstrate any differences in charge selectivity between children with FSGS and MCNS.[29] Since reduction in membrane negative charge in nephrotic syndrome has also been reported to occur in erythrocytes and platelets, and it has been postulated that SSNS may be a generalized disorder affecting cell membrane negative charge.[30]

The podocyte as a vital cell

The role played by podocytes in glomerular function in renal disease and pathogenesis is evolving. Several morphologic changes have been reported in podocytes in nephrotic syndrome. These changes include cell swelling; retraction and effacement of the podocyte foot processes, resulting in the formation of a diffuse cytoplasmic sheet along the GBM; vacuole formation; occurrence of occluding junctions with displacement of slit diaphragms; and detachment of the podocyte from the GBM.[8–10,12,20] These structural alterations in podocytes, often associated with detachment from the underlying GBM, have been shown to result in proteinuria.[9,12,15]

Minimal change nephrotic syndrome

Despite extensive investigation over the last several decades, the pathogenesis of MCNS has remained largely elusive. Several reports have indicated qualitative and quantitative abnormalities in both the humoral and cellular immune systems in MCNS.

Depressed levels of immunoglobulin G (IgG) and increased levels of IgM have been well documented in MCNS.[31] In addition, decreased levels of factor B and factor D have also been noted during relapses.[25] Although these observations indicate an abnormality of B-cell function, in MCNS, their role in the pathogenesis of the disorder is largely uncertain.[31]

Abnormalities in the cell-mediated immune system have long been implicated in the pathogenesis of MCNS. In 1974, Shalhoub first proposed that idiopathic nephrotic syndrome might be due to a disorder of T-lymphocyte function.[32] His hypothesis suggested that a clonal T-cell population might produce a soluble mediator capable of increasing the permeability of the glomerular filtration barrier. Several findings presented to support this view were:

- the disease responded to corticosteroids and alkylating agents
- infections such as measles, which are known to depress cell-mediated immunity, often induced remission
- MCNS had been associated with Hodgkin disease.

A potentially important role of the cell-mediated immune system in nephrotic syndrome is further supported by depressed cell-mediated immunity during relapses of MCNS,[33] alterations in T-cell subsets during relapses,[34,35] and increased cell surface expression of interleukin-2 (IL-2) receptor on T cells, reflecting T-cell activation.[34]

Alterations in numerous cytokines of T lymphocyte origin have been reported in nephrotic syndrome. These abnormalities in cytokine expression include tumor necrosis factor α (TNF-α), vascular permeability growth factor (VPGF), IL-1, IL-2, IL-4, IL-8, IL-10, IL-12, IL-13, and IL-18.[36,37] Despite extensive study of these cytokines, however, none has been shown to be present consistently in MCNS, or has been found to reliably induce significant proteinuria upon injection into animals. Soluble immune response suppressor (SIRS) is another T-cell-derived cytokine isolated from the urine and serum of patients with SSNS.[38–40] Although capable of suppressing both T-cell and B-cell function, it was not found to be present in the urine of patients with SRNS, and was unable to induce proteinuria following injection into animals.

Further evidence suggestive of T-cell involvement in MCNS has been recently described. Screening of genes expressed in peripheral blood mononuclear cells from patients during relapse revealed high levels of NF-κB DNA-binding activity, and reduced expression of IκBα protein, and these abnormalities reversed during remission.[41] These changes are consistent with an increased expression of cytokines by T cells during MCNS, but do not clarify whether the changes are the cause or result of relapse of disease.

Evidence has recently been presented to show that corticosteroids may act directly on the podocytes, rather than through modulation of the immune system. Treatment of cultured podocytes with dexamethasone in concentrations similar to that achieved in the patient's serum during treatment for nephrotic syndrome revealed a dramatic protection against, and enhanced recovery, from podocyte injury.[42] These findings may shed an important light on the pathogenesis of MCNS, and need to be investigated further.

Focal segmental glomerulosclerosis

The pathogenesis of FSGS may be distinct from that of MCNS. FSGS may occur either as a primary or a secondary disease such as in association with reflux nephropathy, hereditary nephropathies, sickle cell disease, HIV nephropathy, obesity, and nephropathy associated with heroin use. The pathogenesis of primary FSGS can be separated into four categories:

- podocyte injury
- genetic mutations
- soluble mediators
- hemodynamic factors.

Podocyte injury

Podocyte injury is now well recognized as a cause for FSGS.[43] Such an injury may occur via immunologic, toxic, or inflammatory pathways, and typically results in effacement or spreading of the podocyte foot processes along the GBM. More severe injury may lead to shedding of podocyte apical cell membranes or detachment of the injured or dead podocyte from the GBM, resulting in podocyturia.[44,45] Since podocytes are believed to be terminally differentiated cells and are unable to replicate, their detachment from the GBM results in exposure of the GBM directly to the urinary space, where it can adhere to the parietal epithelial cell of Bowman capsule. Adherence of these cells to the GBM leads to the formation of a synechia, the earliest 'committed' lesion in the evolution of FSGS. Once synechiae have formed, two self-perpetuating processes begin to take place. The first is the filtration of plasma from functional capillaries into the areas of synechiae and accumulation of plasma proteins underneath the parietal epithelial cell, leading to creation of a periglomerular space. This space allows the filtered proteins to escape into the interstitial tissues and initiate interstitial inflammation. Secondly, the filtered plasma proteins also accumulate in the subendothelial space beneath the GBM, initiating hyalinosis and segmental sclerosis seen in FSGS. Once these two processes have been initiated, the affected glomeruli are at high risk for progressive accumulation of filtrate in the subendothelial and periglomerular spaces, interstitial inflammation and fibrosis, and global sclerosis.[46,47]

Genetic mutations

Mutations in numerous podocyte and podocyte-related proteins have recently been shown to play pivotal roles in the development of SRNS and/or FSGS. These mutations include:

- the slit diaphragm protein nephrin (encoded by NPHS1), which results in the development of congenital nephrotic syndrome of the Finnish type (CNF) in infants[48]
- the podocyte protein podocin (encoded by NPHS2), which results in FSGS in young children[49]
- the Wilms' tumor suppressor gene WT1, which results in Denys–Drash syndrome in children[50,51]
- the actin bundling protein α-actinin (encoded by αACTN4), which results in FSGS in adults[52]
- the LIM-homeodomain protein (encoded by LMX1B), which results in nail-patella syndrome[53]
- the chromatin regulator encoded by SMARCAL1, which results in FSGS associated with Schimke immuno-osseous dysplasia.[54]

Soluble mediators

Soluble mediators also appear to play important roles in some forms of FSGS. Evidence in support of this includes:

- isolation of a 30–50 kDa 'FSGS factor' from the serum of patients with FSGS which is able to induce proteinuria following injection into rats[55,56]
- a marked reduction in proteinuria using protein A immunoadsorption columns[57]
- development of recurrent nephrotic syndrome after transplantation which is also responsive to protein A immunoadsorption, presumably by removing the circulating factor(s).[58]

Additionally, inhibitors of permeability that retard protein permeability through the glomerular capillary have also been isolated from children with recurrent FSGS after renal transplantation. These inhibitors have been identified as apolipoproteins and may imply that an imbalance between permeability promoting factors (FSGS factor) and permeability inhibitors may play a role in the pathogenesis of FSGS.[59]

Hemodynamic factors

Glomerular hypertension has been linked to the development of FSGS. The mechanism by which glomerular hypertension leads to FSGS is proposed to be the capillary stretch and mechanical stress on the podocytes induced by increased transglomerular pressure.[46,47] Although direct in-vivo evidence demonstrating the relationship between mechanical stress and podocyte injury is lacking, mechanical stretch of cultured podocytes has recently been shown to induce their hypertrophy.[60] Repeated or severe stress to podocytes could lead to their detachment from the GBM and initiate the sequence of events discussed above that culminate in the development of FSGS.

Pathophysiology of edema

Edema is the dominant clinical manifestation of nephrotic syndrome in children. Edema, a state of total body water and sodium excess, is the result of fluid accumulation in the interstitial space. The pathogenesis of edema in nephrotic syndrome has been attributed to hypoalbuminemia and an impaired sodium and water excretion.

Hypoalbuminemia

The pathogenesis of edema in nephrotic syndrome and the role of hypoalbuminemia can be understood by examining the

Starling equation, which governs the movement of fluid in the peripheral tissue capillaries:[61,62]

$$\begin{aligned}\text{Net filtration} &= \text{LpS}\,(\Delta\text{hydraulic pressure} - \Delta\text{oncotic pressure})\\ &= \text{LpS}\,[(P_{cap} - P_{if}) - s\,(\pi_{cap} - \pi_{if})]\end{aligned}$$

where Lp is the capillary permeability, S is the surface area of the capillary wall, P_{cap} is the capillary hydrostatic pressure, P_{if} is the interstitial fluid hydrostatic pressure, π_{cap} is the capillary oncotic pressure and π_{if} is the interstitial fluid oncotic pressure, s is the reflection coefficient for proteins (0 = complete permeability and 1 = complete impermeability).

Formation of edema is prevented in healthy individuals by a close balance between forces that favor transcapillary passage of plasma fluid (capillary hydrostatic pressure – P_{cap}) and those opposing it (capillary oncotic pressure – π_{cap}). The net result of these forces, however, marginally favors the passage of fluid from capillary lumen into the interstitial tissue, which is eventually returned into the systemic circulation by the lymphatics. Hypoalbuminemia in nephrotic syndrome results in low capillary oncotic pressure (π_{cap}), and the capillary hydrostatic pressure (P_{cap}) remains relatively unopposed. This change in Starling forces in the peripheral tissue capillary beds favors development of edema.

Sodium and water excretion

Whereas it is well accepted that patients with nephrotic syndrome have an excess of total body sodium and water, there is considerable controversy regarding mechanisms involved in sodium and water retention, as well as the state of their intravascular volume. The 'underfill hypothesis' proposes the existence of a reduced effective circulating blood volume in nephrotic syndrome, whereas the 'overfill hypothesis' proposes the presence of an expanded intravascular volume. Support for both of these views comes from clinical and experimental observations.

Proponents of the underfill hypothesis point to the fact that in the presence of clinical edema, urinary sodium excretion is low in nephrotic patients. It is proposed that low circulating intravascular volume stimulates the renin–angiotensin–aldosterone system (RAAS), and results in renal sodium retention under the influence of aldosterone. Suppression of atrial natriuretic peptide (ANP) additionally contributes to low urinary sodium excretion in these patients.[63] The observation that urinary sodium excretion in nephrotic patients improves following intravenous albumin infusion, or by head-out of water immersion, has been cited as the evidence pointing to sodium and water retention being the consequence of poor intravascular volume. This mechanism may be operative in patients with MCNS.

The overfill hypothesis postulates that patients with nephrotic syndrome have suppression of the RAAS associated with an expanded circulatory blood volume, due to avid sodium reabsorption from the distal convoluted tubule. This distal tubular sodium reabsorption has been suggested to be secondary to ANP resistance.[64] Sodium excretion is not affected by albumin infusion or head-out of water immersion. Some authors have argued that the overfill hypothesis is seen more in animal models of nephrosis than in the human clinical setting.[65]

Because the management of edema in children with nephrotic syndrome will likely differ if patients are deemed volume-expanded as opposed to volume-contracted, establishing whether the patient is 'overfilled' versus 'underfilled' is clinically relevant. One group has advocated measuring the fractional excretion of sodium (FE_{Na}) as well as the relative urinary potassium excretion $[U_K/(U_K+U_{Na})]$.[66] Nephrotic patients with low FE_{Na} (<1%) and high $[U_K/(U_K+U_{Na})]$ (>60%) would fit the profile of a patient with a low intravascular volume, and these urinary tests have been shown to correlate with elevated plasma renin, aldosterone, norepinephrine, and vasopressin levels.[64]

Clinical approach

In a child with periorbital or generalized edema the clinician needs to establish the diagnosis of proteinuria by a dipstick urinalysis. The presence of a $3–4^+$ (300–2000 mg/dl) measurement for protein on a urine dipstick test in the presence of edema establishes a preliminary diagnosis nephrotic syndrome. Proteinuria can be quantified by obtaining urine protein/creatinine ratio in a spot urine sample, and hypoalbuminemia and hypercholesterolemia should be confirmed.

Clinical history

While primary glomerulopathies are usually responsible for childhood nephrotic syndrome, secondary causes associated with systemic diseases may be uncovered by historical data (Table 11.1). The review of systems should focus on extrarenal symptoms that may uncover secondary causes of nephrotic syndrome. Lastly, because nephrotic syndrome can result as a complication of drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), gold, and penicillamine, a thorough review of medication exposure is also crucial.[67]

Physical examination

Hypertension can be seen in children with nephrotic syndrome, but it is more often seen with histologic lesions other than MCNS. The ISKDC data demonstrated that 21% of children (less than 6 years old) with biopsy-confirmed MCNS had systolic hypertension and 14% had diastolic hypertension. This contrasted with children whose nephrotic syndrome was associated with FSGS and MPGN who exhibited systolic hypertension in approximately 50% of cases and diastolic hypertension in roughly 30%.[12] Periorbital edema, ascites, and peripheral edema are also expected findings in nephrotic syndrome.

Table 11.1 Primary and secondary causes of nephrotic syndrome in children

Primary causes

Minimal change nephrotic syndrome (MCNS)
Focal segmental glomerulosclerosis (FSGS)
Mesangial proliferative glomerulonephritis
Membranoproliferative glomerulonephritis (MPGN)/ mesangiocapillary glomerulonephritis:
- MPGN type I
- MPGN type II (dense deposit disease)
- MPGN type III

Membranous nephropathy (MN)

Secondary causes

Systemic diseases associated with nephrotic syndrome:
- Henoch–Schönlein purpura
- Systemic lupus erythematosus
- Diabetes mellitus
- Sarcoidosis

Infectious diseases associated with NS:
- Hepatitis B (usually associated with MN, rarely MPGN)
- Hepatitis C (usually associated with MPGN)
- HIV (often with collapsing variant of FSGS)

Hematology/oncology:
- Leukemia
- Lymphoma (Hodgkin disease usually MCNS)

Sickle cell anemia
Drugs:
- Non-steroidal anti-inflammatory drugs (MCNS)
- Gold
- Penicillamine
- Captopril

Other:
- Bee stings (MCNS)
- Food allergies
- Obesity (usually with FSGS)
- Pregnancy–toxemia

Laboratory evaluation

The laboratory evaluation of children with nephrotic syndrome begins by confirming the presence of hypoalbuminemia, hypercholesterolemia, and assessment of renal function. Mild azotemia is not unusual in childhood nephrotic syndrome. In the ISKDC study, serum creatinine elevation was noted in 32% of children with MCNS, compared with 41% of children with FSGS and 50% of those with MPGN.[12] Macroscopic hematuria is unusual in childhood nephrotic syndrome, but microscopic hematuria is not infrequently seen. Microscopic hematuria was seen in 23% of children with MCNS, in 48% with FSGS, and in 59% with MPGN.[12] Macroscopic hematuria in a patient with nephrotic syndrome should raise the suspicion of renal vein thrombosis.

Serologic evaluation of children presenting with nephrotic syndrome is undertaken to look for secondary causes of nephrotic syndrome. Hypocomplementemia (low serum C3 complement) is seen in MPGN and systemic lupus erythematosus (SLE), as well as in postinfectious glomerulonephritis. Low serum C4 also characterizes SLE. Serum antinuclear antibody (ANA) and anti-double stranded DNA tests can help to establish the diagnosis of SLE.

Additional laboratory tests include screening for viral infections associated with nephrotic syndrome, such as hepatitis B surface antigen and hepatitis B core antibody, hepatitis C antibody, and HIV antibody. A complete blood count (CBC) should also be performed, since abnormalities can be seen in the setting of malignancies (leukemia or lymphoma) as well as in SLE.

Since immunosuppressive therapy is the mainstay of treatment for most forms of childhood nephrotic syndrome, a PPD (purified protein derivative) test to screen for previously undiagnosed tuberculosis is recommended before institution of immunosuppression. Varicella IgG titer to assess the state of immunity may be considered. This can aid in the effective management of varicella-naive patients with varicella zoster immunoglobulin (VZIG), in case of any exposure to the infection.[68] Renal ultrasound is not necessary in the evaluation of childhood nephrotic syndrome. However, in the setting of a child with nephrotic syndrome who develops gross hematuria, a renal ultrasound should be done to exclude the possible development of renal vein thrombosis.

Consideration of renal biopsy

The role of a renal biopsy in children with nephrotic syndrome has long been debated. The clinical indication for a renal biopsy in childhood nephrotic syndrome differs today from historical studies. In the ISKDC studies in the early 1970s, a renal biopsy was performed before the initiation of treatment, but the guidelines for a renal biopsy have become less rigid since then. In current practice, some pediatric nephrologists argue that the decision to biopsy a child with nephrotic syndrome should be age-based, with those older than 10 years undergoing a biopsy because of the higher likelihood of finding a histologic lesion other than MCNS. Others suggest a need for renal biopsy in only those with clinical or serologic suspicion for underlying glomerulonephritis.

Most pediatric nephrologists consider performing a diagnostic renal biopsy in all children with SRNS. An additional indication for a biopsy is to establish 'a baseline' histologic picture before transitioning a child with nephrotic syndrome to an immunosuppressive agent with significant nephrotoxic risks, such as cyclosporine or tacrolimus. Such patients may also require periodic subsequent biopsies to assess for potential treatment-induced nephrotoxicity.

Histologic classification

The development and refinement of the renal biopsy has allowed nephrologists and pathologists to better understand

the natural history and prognosis of nephrotic syndrome by correlating patients' clinical courses with the histologic lesions. The histologic lesions associated with childhood nephrotic syndrome can be separated into glomerulopathies that occur in isolation, *primary glomerulopathies*, and those associated with systemic diseases that accompany the glomerulopathy, *secondary glomerulopathies*.

Primary glomerulopathies

Primary glomerulopathies are those glomerular diseases that are not the result of any underlying systemic disorders. A list of primary glomerulopathies associated with childhood nephrotic syndrome is shown in Table 11.1. The histologic criteria and clinical features of each glomerulopathy will be discussed in detail below.

Minimal change nephrotic syndrome

The histologic definition of minimal change nephrotic syndrome, also known as nil disease, is a renal biopsy specimen featuring no obvious glomerular or tubular abnormalities on light microscopy (Figure 11.1). This lesion, as defined by the ISKDC, permits a slight increase in mesangial matrix or cellularity, an occasional sclerosed glomerulus, or slight tubular atrophy, although the presence of a segmental scar or evidence of glomerular collapse on light microscopy should exclude patients from this category.[69] It is important to note that the histologic lesion of MCNS may in some cases precede the subsequent development of the sclerotic lesion of focal segmental glomerulosclerosis (FSGS). Whether these cases demonstrate a true transformation of MCNS into FSGS, or merely represent the unaffected region of the renal tissue in early biopsies of FSGS, is debatable.

Minimal change disease is the most common histologic lesion seen in children with nephrotic syndrome who undergo renal biopsies at the outset of diagnosis. In the ISKDC study, 77% of the 127 children with untreated nephrotic syndrome who underwent a renal biopsy met the histopathologic criteria of MCNS.[69] Similarly, White et al found that 88% of their unselected children with nephrotic syndrome had MCNS by renal biopsy.[24]

The most representative clinical correlate of biopsy-proven MCNS in an untreated child with nephrotic syndrome is one of a younger-age child, predominantly male, with low likelihood of hypertension and hematuria. In most studies, nearly 80% of children with biopsy-proven MCNS are less than 6 years of age, 60% are male, 13–23% have microscopic hematuria, and 14% have systolic and 21% have diastolic hypertension.[12,24] White et al noted that due to the high incidence of MCNS (77%), a child with new-onset nephrotic syndrome, even if accompanied by hematuria and/or hypertension, was more likely to have MCNS than any other histologic lesion. These investigators reported steroid-responsiveness in 97% of patients, with relapse rates of as high as 94% in steroid-sensitive cases.[25] In the current era, relapse rates are generally lower than in those early reports, primarily due to the longer durations of initial steroid treatments used today.

Focal segmental glomerulosclerosis

Another histologic lesion associated with the childhood nephrotic syndrome is FSGS. This lesion is characterized by scarring within the glomerulus (*glomerulosclerosis*) that is seen in some but not all glomeruli (*focal distribution*). Furthermore, the glomerular scars when present are only seen in a portion of the involved glomeruli (*segmental distribution*) (Figure 11.2). Regional damage to the glomerulus with obliteration of the capillary lumina is associated with a segmental increase in mesangial matrix. One or more lobules of the glomerular tuft may be involved by sclerosis. Formation of segmental

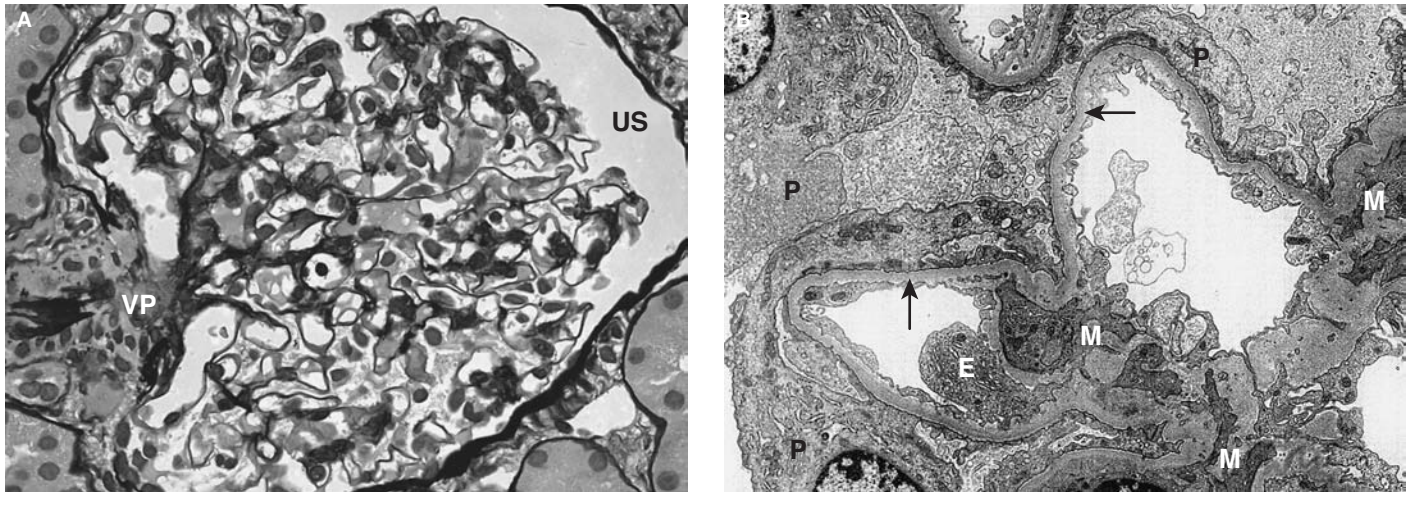

Figure 11.1 Light microscopy showing histologic appearance for minimal change nephrotic syndrome (MCNS). (A) The glomerulus (Jones silver stain) shows normal size and cellularity filling the urinary space (US). The capillary loops are thin and without any deposits. The mesangium is not expanded. The vascular pole is depicted as VP. (B) Electron microscopy showing podocytes (P) with effacement (spreading) of the foot processes over the urinary aspect of the GBM (arrows). The endothelial cells (E) are unremarkable, and the mesangium (M) is not expanded and does not have any deposits or matrix.

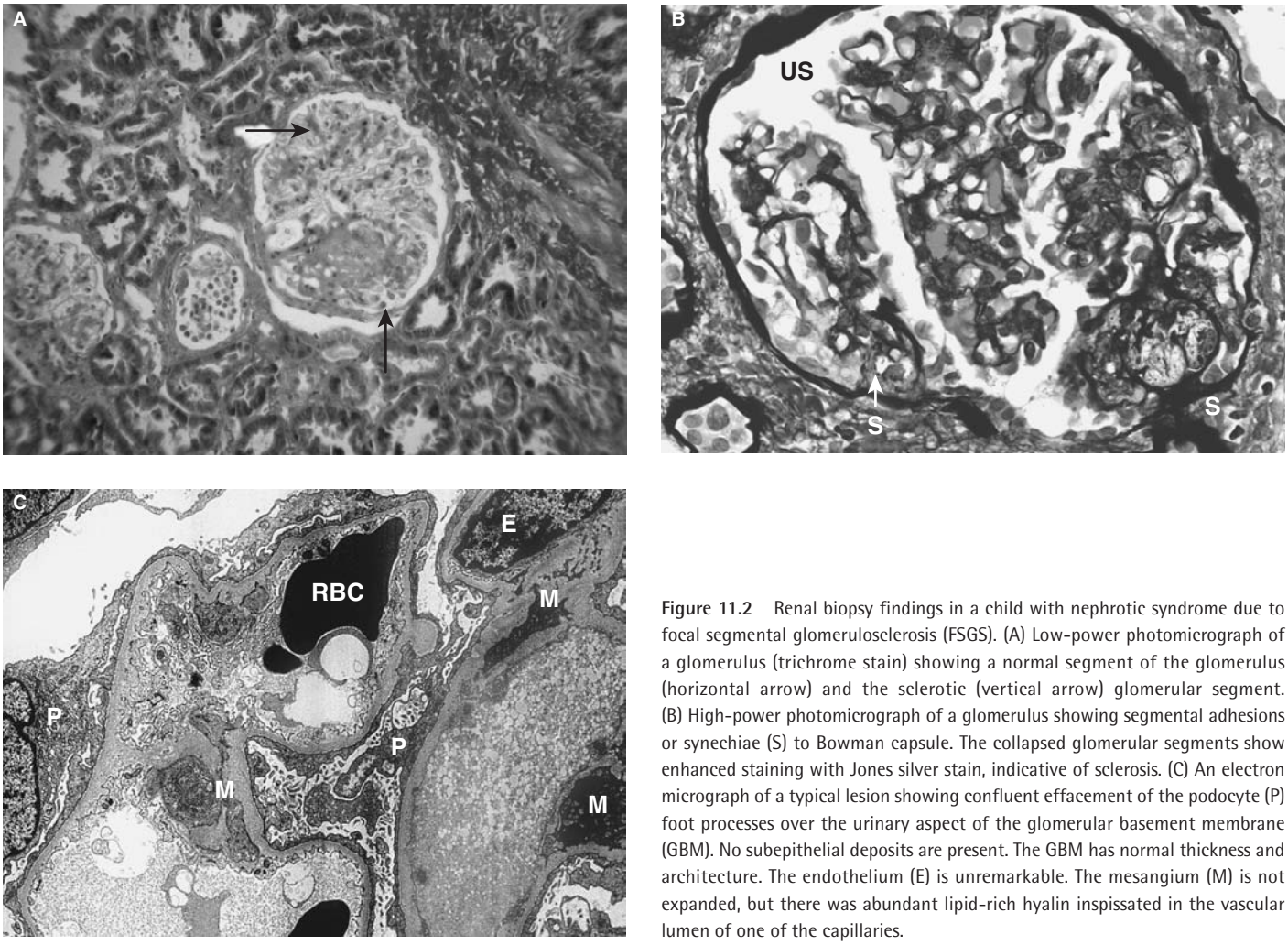

Figure 11.2 Renal biopsy findings in a child with nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS). (A) Low-power photomicrograph of a glomerulus (trichrome stain) showing a normal segment of the glomerulus (horizontal arrow) and the sclerotic (vertical arrow) glomerular segment. (B) High-power photomicrograph of a glomerulus showing segmental adhesions or synechiae (S) to Bowman capsule. The collapsed glomerular segments show enhanced staining with Jones silver stain, indicative of sclerosis. (C) An electron micrograph of a typical lesion showing confluent effacement of the podocyte (P) foot processes over the urinary aspect of the glomerular basement membrane (GBM). No subepithelial deposits are present. The GBM has normal thickness and architecture. The endothelium (E) is unremarkable. The mesangium (M) is not expanded, but there was abundant lipid-rich hyalin inspissated in the vascular lumen of one of the capillaries.

glomerular scars has been proposed to be initiated by formation of synechiae between the glomerular capillary tuft and the parietal cells of Bowman capsule.[70,71]

In early reports, the incidence of FSGS among children with untreated nephrotic syndrome who underwent a renal biopsy ranged from 5 to 9%.[12,24,69] About 50% of these patients were less than 6 years of age, 70% were male, microscopic hematuria and systolic hypertension were seen in nearly one-half of these patients, and one-third exhibited diastolic hypertension. High incidence of resistance to treatment with corticosteroids is well known to be associated with the diagnosis of FSGS. In one study of 12 children with FSGS, 83% of patients were found to be steroid resistant.[24]

Classifying a glomerulopathy as FSGS appears to have some notable limitations. McAdams et al. performed a retrospective clinicopathologic analysis of 134 children with FSGS who presented with nephrotic syndrome or asymptomatic proteinuria. They found that the focal sclerosis lesion can be very nonspecific, and the appearance of the non-sclerotic glomeruli may portend more regarding the disease prognosis. In this study, those children with FSGS and otherwise normal-appearing remaining glomeruli (defined as 'primary FSGS') tended to present with either asymptomatic proteinuria or nephrotic syndrome, were of older age, African-American, and exhibited no disease recurrence post-transplant. Those children with FSGS and generalized podocyte effacement in the non-sclerotic glomeruli were classified in this study as 'minimal change' with FSGS; whereas those with FSGS and mesangial proliferative changes in the non-sclerotic glomeruli were classified as 'mesangial proliferation' with FSGS. Those with FSGS and either minimal changes or mesangial proliferative changes were younger, Caucasian children who presented with nephrotic syndrome and incurred a high risk of disease recurrence post-transplant.[72]

The focal global glomerulosclerosis (FGGS), is a distinct histologic lesion where the sclerosis involves the entire glomerulus, rather than a segmental distribution as seen in FSGS. This lesion appears to be more benign than FSGS, if it occurs by itself and without associated interstitial changes.[73,74]

The collapsing variant of FSGS, or collapsing glomerulopathy, is another glomerulopathy that may be seen in children with nephrotic syndrome. Although the pathogenesis is unknown, this lesion is characterized by marked podocyte hyperplasia

with compression of the glomerular tuft, often mimicking an epithelial crescent formation. The FSGS Working Group's definition of the collapsing variant of FSGS requires at least 1 glomerulus to demonstrate segmental or global collapse and overlying podocyte hypertrophy and hyperplasia.[71] Barisoni et al have demonstrated by immunohistochemistry that biopsy specimens from adults with idiopathic collapsing FSGS and HIV nephropathy showed an abnormal podocyte phenotype. They hypothesized that these 'dysregulated podocytes' may arise as a result of infection.[75] Collapsing glomerulopathy has been reported in patients with HIV infection,[76] parvovirus B19 infection,[77,78] and also as an idiopathic disorder. Its prognosis in adults is significantly worse than that of FSGS.[79]

Finally, FSGS can be either a primary or a secondary disorder. The secondary type of FSGS can be seen in reflux nephropathy, glycogen storage disease, sickle cell disease, and cyanotic congenital heart disease.[80–83] This lesion can also be seen in children with nephrotic-range proteinuria in the absence of nephrotic syndrome. Those patients with FSGS and absence of nephrotic syndrome tend to have a better prognosis compared to those presenting with nephrotic syndrome.[84]

Mesangial proliferative glomerulonephritis

A less common histologic lesion associated with the childhood nephrotic syndrome is mesangial proliferative glomerulonephritis (MesPGN). This glomerulopathy is characterized by increased mesangial matrix and cellularity, but glomerular crescents and adhesions may sometimes be seen. Immunofluorescence is usually negative, but may show mesangial IgM deposition. As has been noted above, FSGS may also accompany this lesion.

The incidence of biopsy-proven MesPGN in untreated children with nephrotic syndrome is approximately 2–5%.[12,24] Clinical features of children with nephrotic syndrome and MesPGN include microscopic hematuria (100%) and hypertension (25%).[85] Garin et al noted in a cohort of 23 patients that nearly 70% were steroid resistant.[86]

Membranoproliferative glomerulonephritis

Another uncommon histologic lesion associated with the childhood nephrotic syndrome is MPGN. Three forms of MPGN have been described based on using immunofluorescence and electron microscopic observations, serology, and by their differing effects on the complement cascade.[87,88] On light microscopy, all forms of MPGN are characterized by an increased mesangial matrix and cellularity, capillary wall thickening, and a characteristic lobular appearance of the glomeruli. Apparent duplication (railroad or tram track appearance) of the GBM due to mesangial interposition is also seen. Immunofluorescence staining is positive for C3 and IgG in MPGN types I and III, and C3 alone are seen in dense deposit disease (MPGN type II). Based on the nature and location of the electron-dense deposits, MPGN is classified into three subtypes. Subendothelial deposits are seen in MPGN type I (Figure 11.3), whereas intramembranous electron-dense deposits characterize dense deposit disease or MPGN type II (Figure 11.4), and transmembranous (subendothelial, intramembranous, and subepithelial), paramesangial, and mesangial deposits have been described in MPGN type III (Figure 11.5).[87,89]

From a clinical perspective, MPGN in early reports accounted for 2–8% of children with new-onset nephrotic syndrome.[12,24,69] Characteristic clinical features of these children included an older age at presentation, a slight female predominance, systolic hypertension in approximately 50% and diastolic hypertension in 25%. Nearly 60% had microscopic hematuria at onset, 75% had hypocomplementemia (low C3), and 50% had azotemia.[12] Often, the clinical presentation is one of nephritic syndrome (macroscopic hematuria, hypertension, and azotemia) in addition to nephrotic syndrome. These patients also tended to respond poorly to corticosteroids.[24,69]

Three types of nephritogenic autoantibodies have been associated with the pathogenesis of various forms of MPGN. Because of their action on the complement cascade, persistently low serum complement C3 is seen in approximately 70–80% of all cases with MPGN. Since the autoantibodies act at different sites along the complement cascade, resultant changes in serum complement C4 and C5 are helpful in differentiating the three subtypes of MPGN. The antibody associated with MPGN type I acts through the classical complement cascade and results in low C3 and C4, with some degree of depression of C5. The antibody associated with type II stabilizes the

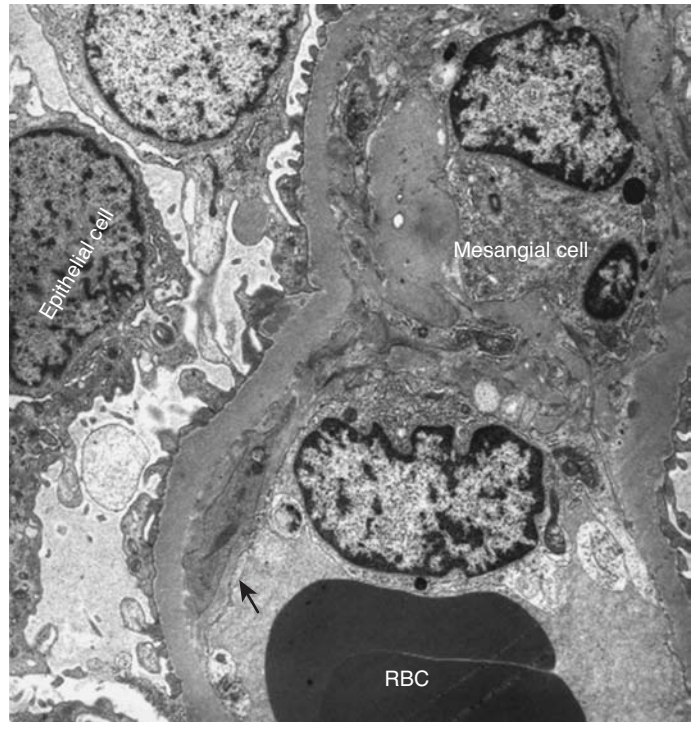

Figure 11.3 Electron micrograph of a patient with membranoproliferative glomerulonephritis (MPGN) type I. The arrow points to the mesangial matrix interposing between the endothelial cell and the glomerular basement membrane (GBM). This results in a thickened appearance of the GBM, with the 'tram track' appearance in light microscopy.

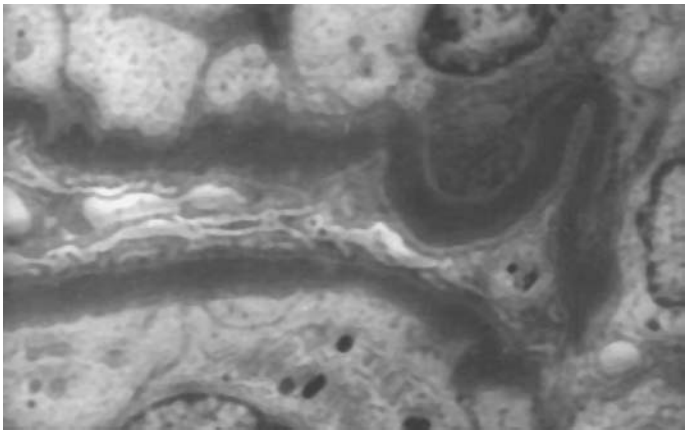

Figure 11.4 Electron micrograph of renal biopsy in a child with membranoproliferative glomerulonephritis (MPGN) type II. Intramembranous dense deposits in a ribbon-like pattern are prominently seen.

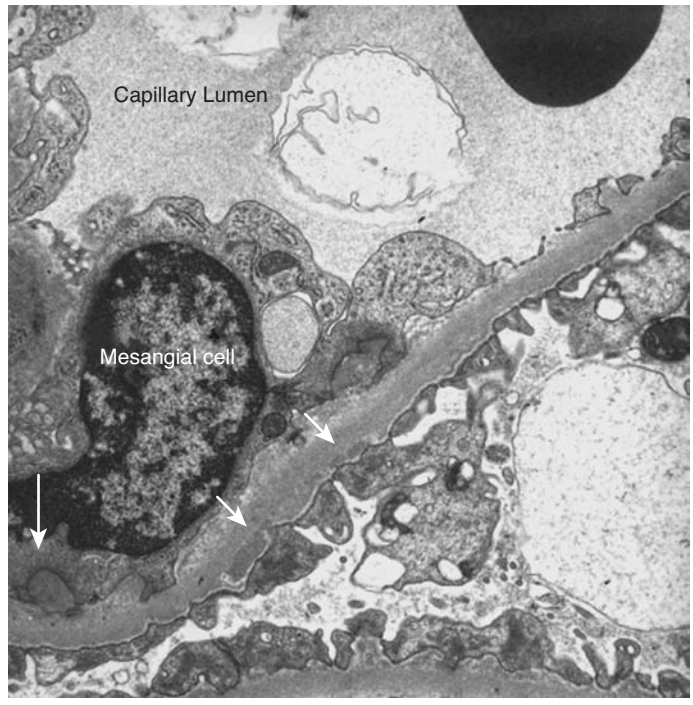

Figure 11.5 Electron micrograph of a renal biopsy in a child with membranoproliferative glomerulonephritis (MPGN) type III. Subepithelial deposits (short arrows) and a solitary subendothelial/paramesangial deposit (long arrow) are seen.

C3 convertase (C3b, Bb), resulting in chronic activation of the alternative complement cascade and very low C3 levels, with normal C4 and C5 levels. The nephritogenic autoantibody associated with type III acts on the terminal cascade, resulting in low C3 and C5 levels, with normal C4 levels.[90]

While primary MPGN is more common, MPGN has also been described as a consequence of other disorders. Both hepatitis B and hepatitis C infections have been associated with MPGN, but these are uncommon in the pediatric age group.[91] It may also be seen in association with chronic bacterial infections, such as ventriculoatrial shunt infection (shunt nephritis) and deep-seated chronic abscesses. Circulating immune complexes appear to be involved in the pathogenesis of MPGN types I and III, and have been seen in patients with shunt nephritis, as well as chronic hepatitis. MPGN associated with partial lipodystrophy is also characterized by hypocomplementemia (low C3) in approximately 70% and C3 nephritic factor in 83% of cases. The median age of onset in one study was 7 years, with females being 4 times more likely to be affected than males.[92] Twenty-two percent of patients developed MPGN within a median of 8 years after diagnosis, and those with renal disease were younger and had hypocomplementemia in 95% of cases.[92] The histologic subtype of MPGN associated with acquired partial lipodystrophy is usually dense-deposit disease (MPGN type II), but other forms have also been described.[93]

Membranous nephropathy

Primary membranous nephropathy or membranous glomerulonephritis (MGN) is the least common histologic lesion seen in childhood nephrotic syndrome. This glomerulopathy is more commonly seen in adults as a cause of nephrotic syndrome. Heymann nephritis is a rat model of human membranous glomerulonephritis. Antibodies directed toward megalin (gp330), a membrane glycoprotein located at the base of the microvilli in the proximal tubular brush border and along the sides and bases of the podocyte foot processes, result in subepithelial immune deposits within the glomerulus.[94,95] The pathogenesis of MGN in humans is unknown, but it is believed to be an autoimmune disorder mediated by immune complexes formed in situ. The antibody responsible for this lesion is probably directed against an antigen within the kidney, resulting in the formation of subepithelial deposits.

The renal biopsy features of MGN on light microscopy demonstrate almost normal glomeruli with diffuse thickening of the glomerular capillary walls. Mesangial proliferation is characteristically absent (Figure 11.6A). Basement membrane stain (silver stain) shows typical 'spikes' on the GBM. Subepithelial and intramembranous electron-dense deposits are characteristically seen on electron microscopy (Figure 11.6B). The subepithelial deposits are eventually incorporated into the GBM and electron-dense deposits may appear predominantly intramembranous in location in the later stages of the disease. Mesangial electron-dense deposits are less common, but have been reported in 31% of children with MGN by the Southwest Pediatric Nephrology Group.[96] Immunofluorescence reveals diffuse granular IgG and C3 staining along the GBM, whereas mesangial immunostaining is negative.

Early studies indicated the incidence of MGN to be less than 3% of all new cases of nephrotic syndrome in children.[24,69] MGN in children is commonly seen in patients with hepatitis B infection.[97] In children with hepatitis B-associated MGN, serologic evidence of Hep B surface antigen (HepBsAg) is

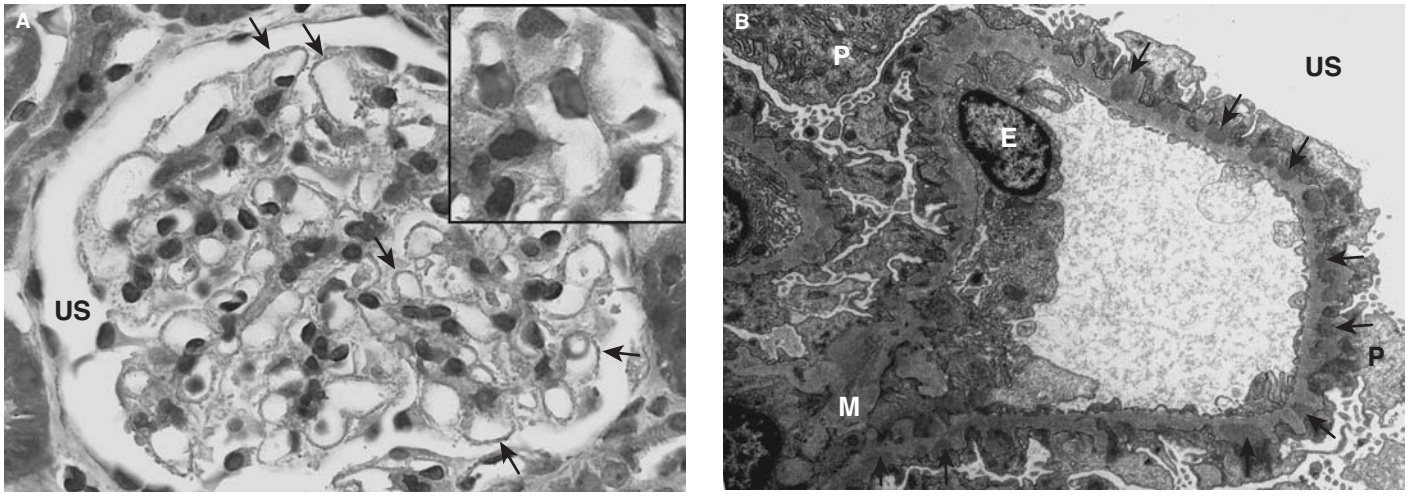

Figure 11.6 (A) Light microscopy renal biopsy findings in a child with membranous nephropathy. A glomerulus (trichrome stain) shows thickening of the glomerular basement membrane (GBM). Subepithelial fuchsinophilic deposits (arrows) are seen. The mesangium is not expanded. Inset shows the details of GBM subepithelial deposits, giving the appearance of 'spikes'. (B) Electron micrographs demonstrating thicked glomerular capillary wall with extensive subepithelial electron-dense deposits (arrows). Spikes are formed by partial enveloping of the deposits by the basement membrane. The podocytes (P) foot processes are effaced.

reported in 100%, hepatitis Be antigen (HepBeAg) in 73%, and hypocomplementemia (low C3) in 31% of cases.[97] Histologically, HepBeAg can be identified in all biopsies of hepatitis B-associated MGN, whereas HepBsAg is not detected consistently. Other common secondary causes of MGN include SLE and drugs such as penicillamine and gold.[98]

Secondary glomerulopathies

Glomerulonephritis associated with an underlying systemic disorder can result in the childhood nephrotic syndrome. These renal lesions are known as secondary glomerulopathies. The histopathology and pathogenesis of the secondary glomerulopathies are variable, depending on the primary inciting process. A list of the secondary glomerulopathies associated with childhood nephrotic syndrome is given in Table 11.1.

Systemic lupus erythematosus

Systemic lupus erythematosus, a multisystem autoimmune disorder, has been reported to be associated with renal involvement in approximately two-thirds of newly diagnosed pediatric cases.[99] The glomerulonephritis associated with SLE can manifest clinically as asymptomatic hematuria and/or proteinuria, acute glomerulonephritis, or nephrotic syndrome.[100,101] It has been estimated that half of children with SLE and renal involvement have nephrotic syndrome.[102] As compared to adults, renal disease is more often present at onset in juvenile-onset of SLE.[99] Renal disease is also usually accompanied by a cutaneous vasculitis and arthritis at the time of diagnosis. Occasionally, the renal disease may be the dominant manifestation of SLE, particularly in an adolescent with non-specific joint pain.

Five histologic subclasses of lupus nephritis are recognized by a classification system proposed by the World Health Organization (WHO), and nephrotic syndrome is most commonly seen with membranous lupus nephritis (WHO class V) and diffuse proliferative lupus nephritis (WHO class IV). Nephritic-nephrotic syndrome (nephrotic syndrome with microscopic or gross hematuria, azotemia, and hypertension) is common in SLE nephritis, especially in the diffuse proliferative disease.

Henoch–Schönlein purpura

Henoch–Schönlein purpura (HSP) is a small-vessel vasculitis, that can be associated with renal involvement. The extrarenal clinical manifestations of HSP include an urticarial or purpuric rash involving the buttocks and lower extremities, joint pain, or abdominal pain. The renal manifestations may consist of microscopic hematuria; acute glomerulonephritis, with or without acute renal failure; and in some cases nephrotic syndrome. Renal biopsies reveal an IgA-associated mesangial glomerulonephritis, with or without crescentic involvement.

Diabetes mellitus

Patients with diabetes mellitus are at increased risk for nephropathy. These patients may also have other glomerular diseases that can coexist with diabetic nephropathy. Diabetic nephropathy resulting in overt clinical disease typically occurs in patients with at least 10 years duration of diabetes mellitus, often with poor glycemic control. Diabetic nephropathy also tends to correlate well with the presence of diabetic retinopathy.[103] Recent observations suggest that the severity of diabetic retinopathy also correlates with preclinical glomerular morphologic changes of diabetic nephropathy.[104] Steroid-sensitive

MCNS, as well as immune complex glomerulonephritis, has also been described in association with insulin-dependent (type I) diabetes.[105,106]

Sarcoidosis

Sarcoidosis is a systemic granulomatous disorder that can be occasionally associated with renal involvement, including nephrotic syndrome. Various glomerular lesions, including MCNS and MGN,[107,108] have been reported in sarcoidosis. Granulomatous interstitial nephritis has also been seen in adults with coexisting membranous nephropathy.[109] Less commonly, renal disease (granulomatous interstitial nephritis) may be the only manifestation of sarcoidosis – also known as renal limited sarcoidosis.

Human immunodeficiency virus infection

Human immunodeficiency virus (HIV) infection can cause nephrotic syndrome in both children and adults.[110] The histologic lesions associated with HIV disease are variable, with the glomerular lesions ranging from mesangial proliferation to that of FSGS. Those cases with FSGS often occur in the setting of nephrotic syndrome and carry a worse prognosis.[111,112] Another glomerular lesion associated with HIV nephropathy is collapsing glomerulopathy. Electron microscopy characteristically reveals tubuloreticular inclusions, which are not specific for HIV infection but are suggestive of the diagnosis. Immune complex-mediated glomerulonephritis has also been reported, and can mimic SLE.[113]

Hepatitis B

Infection with hepatitis B can result in nephrotic syndrome associated with either MGN or MPGN. The clinical picture of children with these histologic lesions can include nephrotic syndrome, acute glomerulonephritis, or a combination of these findings. The MPGN histologic lesion appears to have a higher prevalence in the pediatric age group.[114] Hepatitis B-associated nephropathy in children may be amenable to treatment. Bhimma et al demonstrated clearance of HbeAg, and remission of proteinuria in 10 of 19 children treated with a 16-week course of interferon-α_{2b}.[115]

Hepatitis C

Infection with hepatitis C has also resulted in glomerulopathies, including MPGN and MGN. The MPGN lesion is the most common lesion; it is characterized by immune complex deposition and can be associated with cryoglobulinemia.[116] A combination of interferon-α_{2A} and ribavirin has proven effective for hepatitis C-associated glomerulopathy.[117] Recently, ribavirin monotherapy has also been reported to be successful in inducing remission in a patient with hepatitis C-associated membranous nephropathy.[118]

Viral causes of collapsing glomerulopathy

As discussed earlier, HIV infection should be strongly considered in patients with collapsing glomerulopathy. In addition, other viral infections have been associated with collapsing glomerulopathy, including parvovirus B19, hepatitis C, and CMV infection.[76,119,120]

Leukemia

Acute lymphoblastic leukemia (ALL) has also been associated with the childhood nephrotic syndrome. A few cases of ALL have been reported following treatment for nephrotic syndrome.[121] MCNS has also been reported following hematopoietic stem cell transplant for acute myelogenous leukemia.[122] MGN with nephrotic syndrome has also been described in association with graft-versus-host disease following allogeneic stem cell transplant for chronic myelogenous leukemia in adults.[123]

Lymphoma

Hodgkin lymphoma has been associated with nephrotic syndrome, usually due to MCNS on renal biopsy. Remission of nephrotic syndrome in this disorder usually follows response of the Hodgkin disease, in both adults and children.[124,125]

Non-steroidal anti-inflammatory drugs

Nephrotic syndrome in association with the use of NSAIDs has been well reported. Both MCNS and MGN have been reported in association with NSAIDs.[126,127] Recently, cyclooxygenase 2 inhibitors (celecoxib) have also been reported to cause nephrotic syndrome, which on renal biopsy was associated with minimal change disease and interstitial nephritis.[128]

Angiotensin-converting enzyme inhibitors

Although angiotensin-converting enzyme inhibitors (ACEIs) are commonly utilized for their antiproteinuric effects in patients with nephrotic syndrome and refractory proteinuria, a number of reports have linked nephrotic syndrome to the use of captopril in patients with hypertension. MGN is the usual histologic lesion in captopril-associated nephrotic syndrome.[129]

Miscellaneous drugs

Patients with rheumatoid arthritis may be treated with gold or penicillamine. Both of these medications have been associated with glomerulopathies and proteinuria. MGN comprises nearly three-fourths of the associated renal lesions, although MesGN and MCNS have also been seen.[130] Most cases have been reported in adults, but gold nephropathy has also been reported in a 2-year-old child with juvenile rheumatoid arthritis.[131]

Sickle cell disease

Sickle cell disease may be associated with either glomerular or tubular lesions. Patients with this hemoglobinopathy may occasionally develop nephrotic syndrome. The glomerular lesions associated with sickle cell disease include FSGS and MesGN, with the former more often presenting with nephrotic syndrome.[82] An additional glomerular lesion, sometimes referred to as sickle glomerulopathy, is characterized by mesangial expansion and glomerular basement membrane duplication. Its incidence is estimated to be 4% in patients with sickle cell anemia and it is associated with a high likelihood of progressing to chronic kidney disease.[132]

Obesity

Obesity, defined as a body mass index (BMI) > 30 kg/m^2, has been associated with a glomerulopathy that is FSGS accompanied by large glomeruli, or glomerulomegaly. This condition may present with either nephrotic syndrome, or merely isolated proteinuria. Adults with obesity-related glomerulopathy have been reported to have a slower progression of their renal disease compared with primary FSGS.[133] Obesity-related glomerulopathy has also been reported in adolescents with marked proteinuria without nephrotic syndrome.[134]

Pregnancy

Pre-eclampsia can be associated with either nephrotic-range proteinuria or overt nephrotic syndrome. The prognosis of pre-eclampsia-associated nephrotic syndrome is generally good, as the disease tends not to progress in the postpartum period. Those adults who have undergone renal biopsies have typically been found to have an FSGS-like lesion.[135]

Bee stings

Although rare, bee stings have been reported to be associated with nephrotic syndrome. Tasic reported a young child who developed SSNS after a bee sting, and the patient remained relapse-free for 13 years of follow-up.[136] Others have reported patients with a known diagnosis of nephrotic syndrome who relapsed following a bee sting.[137]

Food allergies

Unrecognized food allergies have also been associated with the nephrotic syndrome. Lagrue et al reported sensitization to food antigens with elevated IgE levels in approximately one-third of 42 patients with nephrotic syndrome.[138] Dietary manipulation, which included the use of a strict oligoantigenic diet, was effective at inducing a remission in patients with SDNS, although subsequent relapses were noted.

Treatment

For the last 50 years, corticosteroids have been the mainstay of therapy for nephrotic syndrome. The majority of children who develop nephrotic syndrome respond to corticosteroid treatment by entering complete remission. Although most pediatric nephrologists initiate corticosteroids immediately following the diagnosis of nephrotic syndrome, spontaneous remissions have been noted in about 5% of cases, usually within the first 8–15 days.[25,39] Consequently, delaying the initiation of corticosteroid treatment has been suggested by some.

The initial episode of nephrotic syndrome in children over 1 year of age is generally treated with high-dose daily oral corticosteroids (prednisone 2 mg/kg/day) for 4–8 weeks. Failure to enter into complete remission following this course of treatment identifies the subset of patients who are at higher risk for potential development of progressive renal disease, and generally prompts consideration of a renal biopsy. In this context, the treatment strategies for nephrotic syndrome are mostly divided into categories based on the child's response to initial oral corticosteroid treatment.

Steroid-sensitive nephrotic syndrome

Steroid sensitivity has been reported in 89% of children with nephrotic syndrome.[24] Approximately 95–98% of children with MCNS are steroid-sensitive, compared with only 20% of those with FSGS.[5,125]

The first widely accepted recommendations for the initial treatment of the childhood nephrotic syndrome came from the ISKDC, and suggested that treatment begin with prednisone at a dose of 60 mg/m^2/day (or 2 mg/kg/day up to a maximum of 80 mg/day) in divided doses for 4 weeks, followed by taper to 40 mg/m^2/day (or 1.5 mg/kg/day up to a maximum of 60 mg/day) for 3 consecutive days per week for the next 4 weeks.[5] The first study by the German collaborative group Arbeitsgemeinschaft fur Padiatrische Nephrologie reported that alternate-day corticosteroids for the second 4 weeks of initial treatment, rather than 3 consecutive days per week resulted in significantly fewer patients with relapses, as well as fewer relapses per patient, than the ISKDC regimen.[140] These authors also found that the alternate-day doses of prednisone could be given as a single daily dose rather than in divided doses. In light of these improved results, this approach subsequently became the dominant treatment regimen for nephrotic syndrome.

A prospective, randomized trial performed later by the Arbeitsgemeinschaft fur Padiatrische Nephrologie compared the efficacy of a 'short term' initial prednisone treatment (the same initial dose as the ISKDC regimen, followed by taper after the urine protein became negative for 3 consecutive days) to the standard ISKDC regimen. This study found that the 'short-term' regimen resulted in a 50% shorter mean duration of remissions, as well as 50% fewer complete remissions at 2-year follow-up, compared with the standard ISKDC regimen.[141]

The apparent effectiveness of longer duration of initial therapy for nephrotic syndrome with corticosteroids was further substantiated in other subsequent studies, where it was demonstrated that use of a longer duration of initial treatment for nephrotic syndrome lasting 12–16 weeks, resulted in both higher rates and longer durations of remission compared with the standard regimen.[142–144] Based on these findings, a prolonged initial course of steroids (6 weeks of daily therapy followed by 6 weeks of alternate-day therapy) is now used by most pediatric nephrologists for children with newly diagnosed nephrotic syndrome, with shorter steroid courses reserved for subsequent relapses. A summary of some selected steroid treatment protocols reported for the initial episode and subsequent relapses of nephrotic syndrome is shown in Table 11.2.

Most children (~75%) enter remission within approximately 2 weeks of initiation of prednisone treatment, and 90–95% of children with responsive disease entering remission within the initial 4 weeks of treatment.[5,145] Only a small percentage of children not responding within the initial 8 weeks enter remission if steroids are continued for up to 12 weeks. This

Table 11.2 Selected corticosteroid treatment protocols for nephrotic syndrome

Authors/reference	Initial episode	Subsequent relapses
Makker and Heymann[147]	Prednisone 2 mg/kg/day (max = 60 mg/day) given tid–qid until urine protein-free × 3 days, then continued × 2 more weeks at same dose, then tapered over 2–4 weeks	Prednisone 2 mg/kg/day (max = 60 mg/day) given tid–qid until urine protein-free × 3 days, then twice the daily dose (max = 80 mg/day) as single a.m. dose on alternate days × 8 weeks, then tapered over 5–6 weeks
ISKDC[6]	Prednisone 60 mg/m^2/day (max = 80 mg/day) given in divided doses × 4 weeks, then tapered to 40 mg/m^2/day given on 3 consecutive days each week × 4 weeks	Prednisone 60 mg/m^2/day (max = 80 mg/day) given in divided doses × 4 weeks, then tapered to 40 mg/m^2/day given on 3 consecutive days each week × 4 weeks (same as initial episode)
Arbeitsgemeinschaft fur Padiatrische Nephrologie[340]	Prednisone 60 mg/m^2/day (max = 80 mg/day) given in divided doses × 4 weeks, then tapered to 40 mg/m^2/48 h (i.e. alternate mornings) × 4 weeks, then tapered	Prednisone 60 mg/m^2/day (max = 80 mg/day) given in divided doses until urine protein-free × 3 days, then tapered to 40 mg/m^2/48 h (i.e. alternate mornings)

contrasts sharply to the effectiveness of prolonged daily steroids (3–6 months) reported to induce remission of nephrotic syndrome in adults.[146,147] Subsequent to entering remission and completion of one of the above initial steroid protocols, the alternate-day oral steroids should be gradually tapered off over approximately 6 weeks (~0.25 mg/kg/dose/week until off). Rapid taper or abrupt discontinuation of steroids greatly increases the risk for early relapse and should be avoided.

Steroid-dependent and frequently relapsing nephrotic syndrome

The majority of children with nephrotic syndrome (50–70%) develop one or more relapses of the disease. These relapses may be transient, with spontaneous remission occurring within 4–14 days in some.[148] Despite prolonged initial steroid use, about 40–50% of those with complete remission of nephrotic syndrome subsequently develop either frequent relapses or steroid-dependence.[141,159] The resultant requirement for additional courses of steroids often leads to the undesirable outcome of an increased overall steroid exposure compared to those with fewer relapses.[141]

Several factors appear to be associated with an increased risk for relapses of nephrotic sundrome. The risk for frequent relapses is generally greater in children who present at less than 5 years of age, and among boys.[150] This risk is particularly high during intercurrent infections, which are the most common causes for relapses of nephrotic syndrome. Indeed, approximately 70% of relapses have been reported to be preceded by an upper respiratory tract infection.[151] A multi-center study in 218 children of a wide variety of factors which might be predictive for frequent relapses in children with MCNS found no correlation between any clinical, histologic (MCNS subgroups), or laboratory findings, and also no correlation with either the time to initial response to steroids or the time between initial response and first relapse.[149] However, this analysis identified a clear correlation between the number of relapses in the first 6 months of diagnosis and the subsequent clinical course. Of those children with no relapses in the first 6 months, 94% had fewer than 3 relapses during the following 18 months. In sharp contrast, of those children with 3 or more relapses during the first 6 months, only 19% had fewer than 3 relapses in the next 18 months, whereas 46% had greater than 6 relapses in the same period.[149] Although early studies suggested that most patients with FRNS had MCNS, one prospective study found that only 4 of 16 (25%) of such children had MCNS, whereas 44% had IgM nephropathy, and 12% had FSGS.[152] Long-term follow-up of these 16 children revealed remission in 10 (62%), persistent proteinuria in 4 (25%), and progression to ESRD in 1 (6%). These findings suggest that, in addition to gender and age at presentation, a child's early pattern of relapses can be helpful in predicting the clinical course over the first 2 years.

Management of relapses generally includes reinstitution of oral daily steroids at a dose of 2 mg/kg/day divided bid (maximum of 80 mg/day) until the urine protein is trace or negative for 3–4 consecutive days, followed by tapering of the steroids to 1.5 mg/kg as a single dose on alternate mornings, and gradual taper over approximately the following 6 weeks (~0.25 mg/kg/dose/week until off). Among children with FRNS, the initial taper to 1.5 mg/kg on alternate mornings is often continued for 2 weeks, and then very gradually tapered off over

5–6 months to try to reduce the frequency of relapses. Even with this approach, however, some children develop relapses either prior to, or within 2 weeks of, discontinuation of the steroids, and are labeled as having SDNS. These children are usually treated in one of two manners. The first approach, proposed by the ISKDC, includes treatment with prednisone at 60 mg/m^2/day until the urine is protein-free for 3 days, followed by taper to 40 mg/m^2/day on alternate days for 4 weeks.[5] A second approach includes treatment with prednisone at 2 mg/kg/day divided bid (or 40–60 mg/m^2/day) until the urine is protein-free for 3–4 consecutive days, followed by taper to 1.5 mg/kg/day every other morning for 2 weeks, and then gradual taper by 0.25 mg/kg/dose every 2 weeks until reaching the lowest alternate-day dose which has historically kept that child in remission (usually 10–20 mg/dose, or 15–20 mg/m^2/dose).[25] This 'prophylactic' dosage can then be continued for anywhere from 6 to 18 months, and then tapered by 0.25 mg/kg/dose every 2 weeks until discontinuation of therapy. In general, this second approach is thought to result in fewer relapses and a lower overall exposure to steroids, although this has not been rigorously verified. The use of low-to-moderate doses of alternate-day steroids is generally not associated with significant side effects, although a decreased growth velocity is sometimes seen in adolescents.[25] Overall, the management strategies above are directed at striking a delicate balance between minimizing the overall steroid exposure for children with SSNS and minimizing the frequency of relapses.

Steroid-sparing agents

Many frequently relapsing and steroid-dependent children either fail to have an adequate response to the above approaches or develop clinically significant side effects of steroid therapy. In this situation, alternative treatments are frequently used. These treatments include the use of cyclophosphamide, chlorambucil, cyclosporine, and levamisole, and more recently mycophenolate mofetil. There is no clear best choice for second line therapy for these children, as cyclophosphamide, chlorambucil, cyclosporine, and levamisole have all been shown to be effective in reducing the risk of relapse at 6–12 months after treatment.[153] However, while the reduction in risk was sustained after the course of treatment for cyclophosphamide and chorambucil, it was not sustained after discontinuation of either cyclosporine or levamisole treatment.

Alkylating agents Although cyclophosphamide (2 mg/kg/day for 8–12 weeks) and chlorambucil (0.2 mg/kg/day for 8–12 weeks) have both been reported to induce long-term remissions in approximately 75% of children with FRNS, both agents are, however, less effective in inducing long-term remissions in children with SDNS, with long-term remissions seen in only 30–35% of children.[154,155] Both of these cytotoxic agents have well-known dose-related toxicities, including leukopenia (~33%), hair loss (2–18%), thrombocytopenia (2–6%), seizures (3.4% – chlorambucil only), hemorrhagic cystitis 2.2% – cyclophosphamide only), severe bacterial infections (1.5–6.3%), malignancies (0.2–0.6%), and fatalities (0.8–1.1%). A recent comparison of these agents by meta-analysis revealed an increased risk for seizures and for severe bacterial infections with chlorambucil compared with cyclophosphamide.[156]

Given the generally similar efficacies of these two agents for FRNS and SDNS, the lower toxicity profile associated with cyclophosphamide has led to it being more widely used in recent years. At cumulative cyclophosphamide doses above 200–250 mg/kg, however, there is a notably increased risk for gonadal toxicity, particularly in males, who appear to be more sensitive than females.[156] Because of this, alternative agents are now usually considered if a single 12-week course of 2 mg/kg day cyclophosphamide (cumulative dose 168 mg/kg) does not induce long-term remission of nephrotic syndrome. More recently, there have been a few reports suggesting that cyclophosphamide can be equally effective, with less risk for toxicity, in both FRNS and SDNS patients, if given as 6 monthly intravenous infusions of 500 mg/m^2/dose compared with daily oral dosing for 12 weeks.[157,158] However, this approach needs to be studied further.

Cyclosporine A Another important alternative agent in the management of these patients is cyclosporine A. Although the mechanism of action of cyclosporine in nephrotic syndrome is not known, the mechanism of action of this immunosuppressive agent is known to involve inhibition of T-lymphocyte activation via inhibition of calcineurin-induced IL-2 gene expression, a critical early event in T-lymphocyte activation.[159] The introduction of cyclosporine to the treatment of nephrotic syndrome has resulted in a marked reduction in the frequency of relapses in steroid-dependent children, with about 85% of children responding to therapy.[160] Unfortunately, many children relapse when the medication is tapered or stopped. A randomized, controlled trial comparing cyclosporine (5–6 mg/kg/day for 9 months and tapered off over 3 months) with cyclophosphamide (2.5 mg/kg/day for 8 weeks) in 73 children and adults with FRNS and SDNS revealed similar efficacy for both drugs at 9 months, but after 2 years only 25% of the cyclosporine-treated patients remained in remission, compared with 63% of those treated with cyclophosphamide.[161] Despite the frequent development of apparent cyclosporine dependency, this medication has proven very useful in reducing the cumulative steroid exposure of children suffering from steroid toxicity.

Cyclosporine therapy can be associated with the development of a variety of side effects. The more common side effects include hypertension, mild increases in serum creatinine, hyperkalemia, gingival overgrowth, and hypertrichosis. However, one of the major drawbacks of the use of cyclosporine is the risk for development of cyclosporine nephrotoxicity, which is manifested as interstitial fibrosis, often in a striped pattern reflective of the vascularization of the interstitium. In a recent study, tubulointerstitial lesions attributed to cyclosporine were found in 11%

of children with MCNS treated with cyclosporine for less than 24 months, but in 58% of those who continued on this medication beyond 2 years.[162] Importantly, interstitial fibrosis can develop without an apparent decline in renal function, and is irreversible.[160] Because of this concern, a renal biopsy is usually performed prior to initiation of treatment, as well as every two years thereafter as long as treatment is continued, to screen for the possible development of interstitial fibrosis. Identification of significant interstitial fibrosis on follow-up renal biopsy should prompt consideration of transition to an alternative therapy from cyclosporine A. In light of this risk for development of irreversible renal injury as a side effect of the treatment of a disease which is potentially reversible, children with FRNS or SDNS in need of alternative therapy should generally be treated first with cyclophosphamide or chlorambucil, prior to consideration of cyclosporine.

Levamisole Levamisole is another alternative agent useful in the management of FRNS and SDNS children.

Levamisole has been reported to prolong the duration of remissions and to have steroid-sparing effects in children with both FRNS and SDNS.[163–166] A recent retrospective comparison between levamisole (6-month treatment) and cyclophosphamide (8–12-week course) in 51 children with FRNS and SDNS found that whereas both treatments reduced the frequency of relapses and total steroid exposure, there was no difference in efficacy between these treatments.[167] With the dosing regimens used in most of the reported trials (2.5 mg/kg on alternate days), levamisole was found to be safe for use in children, with minimal reported side effects.[164,166] Potential side effects of levamisole include flu-like symptoms, neutropenia, agranulocytosis, an erythematous rash, vomiting, seizures, and hyperactivity. As is the case with cyclosporine A, the beneficial effects of levamisole appear not to extend beyond the duration of treatment, which is usually 4–12 months.[164]

Mycophenolate mofetil and mizoribine Mycophenolate mofetil (MMF) and the closely related compound mizoribine have gained popularity in recent years for the management of FRNS and SDNS. Like all of the other treatments described, the mechanism of action of MMF in nephrotic syndrome remains unknown. Despite this, it is known to inhibit lymphocyte DNA synthesis and proliferation via inhibition of a key enzyme in purine biosynthesis, inosine monophosphate dehydrogenase (IMPDH).[168] In addition, MMF interferes with adhesion of activated lymphocytes to endothelial cells via inhibition of glycosylation of adhesion molecules.[169] Clinically, these effects are selective for T and B lymphocytes, because all other cells have a 'salvage pathway' by which purines can still be synthesized in the presence of MMF.[170] It is unclear if MMF works in nephrotic syndrome via the above-mentioned immunosuppressive pathway.

Mycophenolate and mizoribine have been used successfully to reduce proteinuria and stabilize renal function in a variety of glomerular diseases, primarily in adults.[171,172] However, several reports have also demonstrated their effectiveness in reducing the frequency of relapses in children with FRNS and SDNS.[173–176] These studies have demonstrated that MMF permits a significant reduction in total steroid exposure. Interestingly, one study found that mizoribine was more effective in children below 10 years of age.[173] The typical treatment dose used for MMF has been about 600 mg/m^2/dose given twice daily (maximum dose of 1000 mg bid in adult-sized patients). Most patients have not had serious side effects in these reports. However, the side effects of MMF and mizoribine include nausea, vomiting, diarrhea, constipation, headache, edema, bone marrow suppression, anemia, gastrointestinal bleeding, and hyperuricemia (for mizoribine). Based on the above findings, MMF is increasingly being recognized as a safe and effective alternative agent in the management of children with FRNS and SDNS.

Steroid-resistant nephrotic syndrome

Despite optimal management of nephrotic syndrome, approximately 10% of children will prove to be steroid-resistant and require alternative therapies. Before concluding that the patient is steroid-resistant, it is important to verify adherence to the treatment regimen, consider whether the patient is able to absorb the medication, rule out underlying infection, and consider the possibility of occult malignancy. This failure to enter remission in response to an 8-week course of oral prednisone may be present from the initial disease presentation (primary steroid resistance) or may develop among children who had previously had SSNS (secondary steroid resistance). In either situation, development of resistance to steroid therapy identifies children at dramatically increased risk for both the development of extrarenal complications of nephrotic syndrome and for the development of ESRD. Indeed, it is estimated that the risk for development of CKD or ESRD in this population is more than 40% within 5 years from the time of diagnosis.[150] In addition SRNS is the underlying cause for more than 10% of all children who develop ESRD.[177]

Given these ominous statistics, a variety of alternative therapies have been utilized to try to induce remission and thereby reduce the risk for development of ESRD. Unfortunately, since the majority of the data available have been from anecdotal reports or uncontrolled clinical trials, it is difficult to directly compare many reports or to generalize the findings for all children with SRNS. This has understandably led to a lack of consensus among pediatric nephrologists about the optimal treatment for SRNS. A recent survey of pediatric nephrologists about treatment of FSGS revealed significant variability in the therapeutic approach.[178] This study found that by 1999, cyclosporine had become the most widely used alternative therapy for these patients, with 73% using it often, or sometimes. In contrast, only 44% reported using the previously published intravenous methylprednisolone and oral alkylating agent

protocol (Tune–Mendoza protocol), at least sometimes, with 27% never using this protocol, while 60% used oral cytotoxic agents often or sometimes. Importantly, this study also revealed that among non-immunologic therapies, 92% of the pediatric nephrologists were treating their patients with ACEIs, whereas only 31% were using lipid-lowering agents to treat the hyperlipidemia associated with refractory nephrotic syndrome. Within the last 2 years, a large prospective multi-center controlled trial in children and young adults with FSGS has been started to compare the efficacy in inducing remission of cyclosporine to combination therapy with oral pulse dexamethasone and MMF (www.bio.ri.ccf.org/Research/fsgs/).

A list of the treatment options that have been used in the management of SRNS in children is shown in Table 11.3. In general, the management of SRNS can be divided into four major categories:

- supportive therapy
- immunosuppressive therapy
- immunostimulatory therapy
- non-immunosuppressive therapy.

Supportive and adjunctive therapies

Supportive therapy includes meticulous general medical care, dietary adjustments, alteration of immunizations, management of edema, and management of hyperlipidemia. A summary of the components of each of these aspects of care is shown in Table 11.4.

Table 11.3 Treatment options for children with SRNS

Immunosuppressive	Immuno-stimulatory	Non-immunosuppressive
Pulse IV methylprednisolone	Levamisole	ACE inhibitors
Alkylating agents (cyclophosphamide, chlorambucil)		Vitamin E
Cyclosporine A		Non-steroidal anti-inflammatory drugs*
Tacrolimus		Pefloxacin*
Mycophenolate mofetil		
Plasma exchange and immunoadsorption*		
Azathioprine*		
Mercaptopurine*		
Vincristine*		

*, Less commonly used or controversial.

General medical care

Careful general medical care plays an important role in the management of children with refractory nephrotic syndrome. Cutaneous infection and cellulitis can rapidly evolve in an edematous patient with nephrotic syndrome and skin breakdown should be prevented. Development of pain or asymmetric swelling of an extremity, respiratory distress, acute oliguria or gross hematuria, or neurologic symptoms may indicate venous vein thrombosis. Abdominal pain may be due to peritonitis and needs prompt attention. Hypovolemia and hypotension responsive to intravascular volume expansion by a colloidal solution, such as intravenously administered albumin, can be seen, especially with an intercurrent illness. Intravenous albumin infusions can be complicated by the acute development of hypertension or respiratory distress if infused too rapidly.[179]

Immunizations

Each patient should undergo tuberculin testing with a PPD test or tine test to exclude tuberculosis. Identification of this or any other infection should prompt initiation of treatment of the infection prior to initiation of steroid therapy. In addition, verification of immunity to varicella should also be performed prior to initiation of steroid therapy, since prolonged immunosuppression increases the risk for development of a serious or even life-threatening disseminated varicella infection, following exposure.

In general, routine immunizations (including varicella), in children with nephrotic syndrome should usually be delayed until the child has entered stable remission and been tapered to low-dose alternate-day steroids, since the response to immunization can be suboptimal in immunosuppressed patients.[180,181] Immunization with live virus vaccines is not recommended by the American Academy of Pediatrics for patients who have received corticosteroids – in a dose of 2 mg/kg/day of prednisone or its equivalent for more than 14 days – until the patients have been off of steroids for at least 4 weeks. In contrast, children who are on lower doses of steroids (less than 2 mg/kg/day) or alternate-day steroids can generally receive live virus immunization during steroid treatment.[182] For non-immune children exposed to varicella while on immunosuppressive therapy, prophylactic VZIG is recommended to prevent or minimize the severity of infection.[68] To be effective, however, it must be given within 96 hours after exposure, and earlier treatment is more efficacious.

Although there is a rare risk for induction of relapses by immunizations,[183] children with nephrotic syndrome being treated with either no or alternate-day steroids can be effectively immunized with relatively little risk. This was recently demonstrated in a multi-center study of the immunization of 29 nephrotic children with a two-dose regimen of varicella vaccine, 45% of whom were receiving alternate-day prednisone at doses up to 1.6 mg/kg.[184] These authors reported a 100% seroconversion rate, with 91% retaining protective levels of antibody for 2 years, and no adverse events. Thus, there does not appear to be a contraindication to immunization in most

Table 11.4 Components of supportive therapy for children with SRNS

General medical care	Management of edema	Management of hyperlipidemia
Identification and treatment of suspected thrombosis: • Asymmetric swelling in extremity • Respiratory distress • Acute oliguria • Gross hematuria • Neurologic symptoms	Avoidance of excessive fluid intake	Avoidance of high fat intake
Identification and treatment of suspected infection: • Cellulitis • Peritonitis • Sepsis	Moderate restriction of dietary salt	Regular exercise regimen (30–45 minutes of moderately intense exercise daily)
Maintenance or restoration of intravascular volume	Elevation of extremities	Use of HMG CoA reductase inhibitors (statins)
Maintenance of adequate protein intake (130–140% of RDA)	Judicious use of diuretics (only for severe edema)	LDL apheresis
Alteration of immunizations	Head-out water immersion	

children with nephrotic syndrome (i.e. those on no or alternate-day steroids), since most can be expected to respond to routine immunizations, and the benefits of immunization generally far outweigh the risks of relapse.

Management of edema

General strategies for the management of edema in nephrotic syndrome include moderate fluid restriction, salt restriction, and the judicious use of diuretics. Additional dietary recommendations include maintenance of reasonable protein intake of 130–140% of the recommended daily allowance (RDA) for age, and avoidance of saturated fats, as this may worsen the hyperlipidemia.[177]

Relief of severe anasarca or disabling edema can be achieved by initiating intravenous 25% albumin infusion at a dose of 1 g/kg/dose, given over 3–4 hours, followed immediately by furosemide challenge (1–2 mg/kg/dose). This therapy may be cautiously repeated in severely edematous patients. The risk of aggressive albumin infusion therapy is sudden mobilization of subcutaneous tissue fluid into the intravascular compartment, pulmonary edema, and congestive cardiac failure.[179] In general, gradually increasing the serum albumin level to approximately 2.8 g/dl is adequate to restore intravascular oncotic pressure and volume, and little additional clinical benefit results from increasing the albumin level to normal values.

The most commonly used diuretic is the loop diuretic, furosemide. This drug acts by inhibiting the sodium-potassium-2 chloride transporter in the thick ascending limb of the loop of Henle. Several factors, however, may impair the efficacy of furosemide during nephrotic syndrome. Since loop diuretics are highly protein bound, preventing their filtration in the glomerulus, furosemide acts via delivery to the vascular side of proximal tubular cells bound to albumin, where it is taken up and secreted into the tubular lumen for delivery to the loop of Henle.[185] The presence of hypoalbuminemia, however, may result in reduced delivery of albumin-bound furosemide to the proximal tubular cells for secretion. Hypoalbuminemia also causes an increased volume of distribution of furosemide, due to diffusion of the free drug into the expanded interstitial compartment.[185] Yet another potential cause for the observed tubular resistance to furosemide results from significant proteinuria, whereby urinary albumin can bind to furosemide within the tubular lumen and reduce the free drug available at the site of action.[185]

A variety of approaches have been developed to overcome the resistance to furosemide, including increased diuretic dosage, co-administration with albumin, and co-administration with distal tubular diuretics (thiazides). The use of dosage ranging from 200–300% of normal can often achieve the desired clinical effects, although high doses in the presence of unresponsive oliguria greatly increase the risk for ototoxicity, which has been correlated with high peak furosemide levels.[186] Common clinically effective dosing regimens for intravenous furosemide in nephrotic children with normal renal function range from 0.5–1 mg/kg Q6–12 h. However, several reports in children without nephrotic syndrome have documented that continuous infusion of furosemide results in a more efficient diuresis compared to intermittent administration.[187–9] An alternative approach is the co-administration of furosemide with albumin, which has been reported to improve furosemide efficacy by expanding the intravascular volume, resulting in

improved renal perfusion and drug delivery to the kidney.[179,189] Yet another approach to improve the clinical efficacy of furosemide in nephrotic syndrome has been co-administration with the thiazide-type diuretic, metolazone, which has actions primarily in the distal tubule but has some secondary effects on the proximal nephron, or with a classic thiazide.[190] This approach has been suggested to produce synergy by inhibition of sodium reabsorption at multiple sites in the nephron.[191,192] It is important to remember that although these strategies can improve the efficacy of furosemide in the setting of nephrotic syndrome, they also increase the risk for inducing complications, as evidenced by the recent identification of furosemide as the major iatrogenic risk factor for the development of thrombosis in children with nephrotic syndrome.[193] In addition, loop diuretics have been associated with several other side effects, including electrolyte disturbances such as hypokalemia and metabolic alkalosis, hypercalciuria, nephrocalcinosis, and ototoxicity.[189] Based on these concerns, chronic outpatient use of diuretics in children with nephrotic syndrome is generally avoided. Thus, although diuretics can be a very important part of the management of severe edema in nephrotic syndrome, the risks associated with this therapy should be kept in mind for both chronic outpatient and aggressive inpatient use of diuretics.

Lastly, non-pharmacologic management of edema can also be clinically useful. The edema in nephrotic syndrome is gravity-dependent, appearing most commonly as periorbital or back edema upon awakening, with gradual shifting of the fluid to the lower extremities over the day while the child is upright. Since the edema develops due to decreased intravascular oncotic pressure, elevation of the extremities to the level of the heart or higher increases the tissue hydrostatic pressure. This returns fluid to the intravascular space and thus reduces the edema. Another safe and effective alternative for the management of edema, although not commonly practiced, is the use of head-out water immersion.[194] This treatment was found to induce a potent diuretic and natriuretic response, with significant increases in central blood volume and urine output, and reductions in plasma arginine vasopressin, renin, aldosterone, and norepinephrine levels.

Management of hyperlipidemia

Hyperlipidemia is an almost universal clinical finding in children with nephrotic syndrome. The lipid profile in nephrotic syndrome is characterized by elevations in total plasma cholesterol, very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) cholesterol, and often triglyceride levels, as well as variable alterations (more often decreased) in high-density lipoprotein (HDL) cholesterol.[195] In addition, significant increases in plasma levels of lipoprotein A [Lp (a)], which is known to be both atherogenic and thrombogenic, are also often seen in children with proteinuria.[196] Although in patients with SSNS the hyperlipidemia resolves gradually upon developing a remission, children with SRNS who are refractory to therapy are often exposed to prolonged hyperlipidemia and its associated risks.

Chronic hyperlipidemia has been clearly associated with an increased risk for cardiovascular complications in adults,[197] and may contribute to progressive glomerular damage in pre-existing renal disease.[198–201] Moreover, adults with nephrotic syndrome have a significantly increased relative risk for myocardial infarction (RR = 5.5) and coronary death (RR = 2.8) compared to the general population,[202] and cardiovascular complications due to atherosclerosis are the leading cause of death in the adult dialysis and transplant population.[195] In this light, treatment of hyperlipidemia in children with refractory nephrotic syndrome offers the potential for reducing the risk for disease progression, as well as reducing the risk for cardiovascular complications later in life.

A few uncontrolled trials have demonstrated the potential usefulness of hydroxymethylglutaryl CoA (HMG CoA) reductase inhibitors (statins) in children with SRNS. The first study analyzed the effects of treatment with simvistatin in 7 children (ages 1.8–16.3 years; mean = 8 years) and found a 41% reduction in cholesterol and 44% reduction in triglyceride levels within 6 months of treatment, which persisted in the majority of children (71%) until 12 months and was well tolerated.[203] The second study analyzed 12 children (0.8–15 years) treated with simvistatin or lovastatin for 0.8–5 years (mean = 2.7 years) and found a marked reduction within 2–4 months in total cholesterol (40%), LDL cholesterol (44%), and triglyceride (33%) levels, but no significant changes in HDL cholesterol levels.[204] Treatment was found to be very safe, with no associated adverse clinical or laboratory events. Despite this apparent efficacy, however, the authors found no significant improvement in proteinuria, hypoalbuminemia, or rate of progression of underlying disease during the 1–5 year (mean = 2.7 years) follow-up period. Although the long-term safety of statins in children has not yet been established, statin therapy is generally well-tolerated in the general population, and appears to be similarly well-tolerated among adults with nephrotic syndrome, in whom only mild asymptomatic increases in liver function tests and creatinine kinase, and one case of diarrhea have been reported.[205] Despite these findings in adults, a recent comprehensive review on the potential role of statin therapy in pediatric nephrotic syndrome has emphasized the need for randomized, placebo-controlled studies to be performed to clarify the efficacy and safety of statin therapy in pediatric nephrotic syndrome.[206]

Another approach to the management of hyperlipidemia in refractory nephrotic syndrome is the use of LDL apheresis. A prospective uncontrolled trial of LDL apheresis + steroid treatment in 17 patients with FSGS revealed significant decreases in serum total cholesterol and a significant increase in serum albumin, which was associated with significantly reduced proteinuria and induction of either partial (33%; 4 of 12 patients) or complete (67%; 8 of 12 patients) remission of nephrotic syndrome in 70% of patients (12 of 17 patients).[207] A subsequent study in 11 children with steroid-resistant, cyclosporine-resistant nephrotic syndrome due to FSGS examined LDL apheresis administered as 12 treatments over 9 weeks with prednisone added in weeks 4–9, and found that 7 children (63%) entered

into either complete (45%; 5 of 11 children) or partial (18%; 2 of 11 children) remission.[208] After an overall mean follow-up of 4.5 years, all five (100%) of those children who entered complete remission after LDL apheresis remained in remission with normal renal function, while all four of those who failed to respond to treatment progressed to ESRD in a median time of 1.3 years. Another recent prospective study compared LDL apheresis to no pheresis among 18 adults with nephrotic syndrome due to diabetic nephropathy.[209] These authors found that, compared to the no pheresis group, LDL apheresis was associated with significant reductions in total serum cholesterol, LDL cholesterol, and lipoprotein A, as well as proteinuria and urinary podocyte excretion. Similar to the previous report, response to apheresis was also associated with a significant increase in creatinine clearance. Together, these studies suggest that in addition to its ability to ameliorate the hyperlipidemia seen in nephrotic syndrome, LDL apheresis may be a reasonable alternate strategy to try to induce at least a partial remission in children with refractory nephrotic syndrome.

Immunomodulatory therapies

The early identification and treatment of complications, management of edema and hyperlipidemia, alterations of immunizations, and dietary considerations described above are all essential to optimize the supportive management of children with refractory nephrotic syndrome. However, the primary effort in the management of children with SRNS should be directed at induction of remission. The treatments that have been used to try to induce remission in these children can be divided into immunosuppressive, immunostimulatory, and non-immunosuppressive therapies (see Table 11.3).

Pulse intravenous methylprednisolone

Methylprednisolone pulses have been used for many years in the management of SRNS. The most widely known protocol for IV pulse methylprednisolone was first proposed by Mendoza and Tune in 1990[210] and included IV methylprednisolone (30 mg/kg) in the following schedule: Alternate days for 2 weeks, then weekly for 8 weeks, then every other week for 8 weeks, then monthly for 9 months, then every other month for 6 months. This treatment was accompanied by oral prednisone, and if needed, cyclophosphamide or chlorambucil. In this initial report they found that after 46 months of follow-up, 12 of 23 children (52%) were in complete remission, and an additional 6 children (26%) had mild to moderate proteinuria, with all 18 of these responders (78%) retaining normal renal function. A subsequent report by this same group described the long-term follow-up (mean = 6.3 years) of 32 children with steroid-resistant FSGS treated with this protocol, and found that 21 children (65.6%) were in complete remission, 3 (9.4%) had mild proteinuria, 2 (6.2%) had moderate proteinuria, and 6 (19%) remained nephrotic.[211] Although 25 children (78%) had also received an alkylating agent as part of the protocol, all of those who entered remission had no loss of renal function. Importantly, the reported side effects included cataracts (22%), impaired growth (17%), hypertension (17%), leukopenia (19%), and gastrointestinal distress which was common.[210,211]

Despite the initial success reported with this protocol, its use became somewhat controversial after other investigators were unable to reproduce these response rates. Differences in the protocols used and in the patient populations may have been in part responsible for these differences. However, complete remission rates ranging from 38–82% have been reported in several subsequent studies, with similar or lower incidences of side effects compared to that of Mendoza and Tune.[212–216] Although these responses have been impressive, and the reported side effects reasonably modest, the use of IV pulse methylprednisolone remains controversial among pediatric nephrologists, due primarily to remaining concerns about the long-term side effects of corticosteroids in children. Given the reported clinical results, however, IV pulse methylprednisolone offers among the highest reported rates of remission for the treatment of SRNS.

Alkylating agents

Alkylating agents such as cyclophosphamide and chlorambucil have been widely used in the treatment of SRNS. A report from the ISKDC,[217] as well as some other subsequent reports have found these agents to be generally ineffective in inducing remissions in this group of patients, with either no improvement in remissions compared to prednisone alone or a low rate of complete remissions.[218,219] Despite this, one study noted a high rate of partial remissions (45%) and reduced risk of progression to ESRD among children treated with cyclophosphamide.[218] Interestingly, one report noted that among 4 children with SRNS who had entered remission after 2 courses of alkylating agents, subsequent relapses for all 4 children were not only infrequent, but also had become steroid-responsive again.[220]

Over the past 10 years, investigators have gravitated toward the use of IV rather than oral cyclophosphamide. The rationale for this was initially founded on a small randomized prospective controlled trial in 13 children with SRNS comparing alternate-day oral steroids combined with either oral or 6 monthly IV pulses of cyclophosphamide.[221] These investigators found that compared to those treated with oral cyclophosphamide, those treated with IV cyclophosphamide received a lower cumulative dose of therapy, yet had a dramatically higher rate of complete remission (100% vs. 17%), as well as longer periods without proteinuria and fewer significant side effects. Subsequent studies have reported variable responses to 6 monthly IV pulses of 500 mg/m^2 cyclophosphamide. Although one study reported achievement of complete remission in 7 of 10 (70%) South African children with SRNS,[222] a subsequent study using the same dose of cyclophosphamide in 5 Saudi Arabian children reported no complete remissions, and only 3 partial remissions (60%), leading them to question the efficacy of this protocol.[223] Importantly, these were both small studies and conducted in different ethnic groups, which may have influenced the results. In addition, the prednisone dosage used during these trials was different, with the more favorable results obtained in

the trial that included concurrent initial use of daily, rather than alternate day, steroids.

Two reports have highlighted the potential clinical importance of primary versus secondary steroid resistance in the likelihood of response to IV pulse cyclophosphamide therapy. The earlier study evaluated 5 children who had primary steroid resistance and 5 who had developed secondary steroid resistance who were treated with 6 monthly IV pulses of 500 mg/m^2 of cyclophosphamide.[222] These authors found that despite a 70% complete remission rate, all 5 children with secondary steroid resistance (100%) entered complete remission, while only 2 with primary steroid resistance (40%) entered complete remission during the trial. A more recent, larger study prospectively evaluated 6 monthly IV pulses of a larger dose of cyclophosphamide (750 mg/m^2) in 18 children with primary steroid resistance and 6 children who developed secondary steroid resistance.[224] These authors similarly found a 50% complete remission rate among those with secondary steroid resistance, compared to only 22% of those with primary steroid resistance. Of interest, 86% of those who entered complete remission, and 57% of those who entered partial remission, did so within the first 2 months of treatment. Together, these reports suggest that primary steroid resistance increases the risk for unresponsiveness to IV cyclophosphamide compared to those children who develop steroid resistance later in their clinical courses.

Chlorambucil has also been reported to have some efficacy in treating SRNS in children. A prospective study of an 8–16-week treatment of this medication (0.2 mg/kg/day) in a subset of 5 children with both steroid and cyclophosphamide resistance revealed that 4 children (80%) achieved complete remissions, and only 2 of these children (40%) developed subsequent relapses.[225] Together with the results noted above for cyclophosphamide, these findings suggest that both monthly IV cyclophosphamide pulses for 6 months and oral chlorambucil continue to have significant potential utility in the management of children with SRNS.

Cyclosporine A

In retrospective studies, cyclosporine A was found to be clinically beneficial in approximately two-thirds of children with SRNS. A recent review reported that cyclosporin A use in children with SRNS induced a complete remission in 52%, and a partial remission in an additional 12%.[150] Two randomized, controlled trials evaluated the efficacy of cyclosporine in SRNS.[226,227] In the first study 45 adults and children were randomized to receive either supportive therapy or cyclosporine for 6 months, followed by a gradual taper over 6 months.[226] After one year the authors noted that 13 of 22 (59%) cyclosporine-treated patients, compared to 3 of 19 (16%) control patients had entered into complete remission. Among the 10 children included in this study, 40% entered into complete remission, and another 20% had a partial remission. In the second study, 25 children with biopsy-proven FSGS were randomized to receive either cyclosporine or placebo for six months.[227] After the 6 months the authors found that 4 of the 12 children (33%) treated with cyclosporine entered into complete remission, while the remaining 8 children (67%) had a partial remission. In contrast, none of the 12 who received placebo entered into complete remission and only 2 (17%) had a partial remission. Consistent with these findings, a recent meta-analysis of all randomized controlled trials for the treatment of childhood SRNS found that, compared to placebo or no treatment, treatment with cyclosporine resulted in a relative risk for persistent nephrotic syndrome of 0.69 (95% Confidence Intervals (CI) 0.47–0.88)).[228] Thus the available literature overall suggests that cyclosporine is similarly effective to IV pulse methylprednisolone therapy in the management of SRNS, and is thus among the most effective therapies currently available for the management of this disease.

Despite its effectiveness, cyclosporine has a number of potentially important side effects that can limit its usefulness. As noted in the section above on FRNS, cyclosporine therapy can be associated with a variety of side effects, including nausea, vomiting, headaches, hypertension, mild increases in serum creatinine, hyperkalemia, gingival overgrowth, and hypertrichosis. Its most worrisome side effect, however, development of irreversible interstitial fibrosis (cyclosporine nephrotoxicity), is of particular importance in the steroid-resistant population. Approximately 42% (range 10–86%) of children in whom remission is successfully induced with cyclosporine develop relapses, either during tapering or withdrawal of the medication, leaving them cyclosporine-dependent and increasing the risks for interstitial fibrosis.[150,229] Several reports have documented this increased risk, reporting incidences of interstitial fibrosis of 35–79%.[162,230–232] However, one recent report that included treatment of 20 adults and children with cyclosporine for more than 4 years found no clear cyclosporine-induced interstitial fibrosis.[233] While it should be noted that it is difficult in some cases to discern whether the development of interstitial fibrosis is due to the effects of cyclosporine or progression of the underlying disease, in at least one study the incidence of fibrosis was notably higher in a cyclosporine-treated group compared to a non-cyclosporine-treated group.[231] Because steroid-resistant patients often require long-term cyclosporine use, it is important to note that the risk for interstitial fibrosis appears to increase with increasing duration of therapy. A recent study of 37 children found that only 11% of children treated with cyclosporine for less than 24 months had interstitial fibrosis, as compared to 58% of those treated with cyclosporine for more than 24 months.[162] In addition to duration of treatment, other factors which have been found to correlate with increased risk for cyclosporine nephrotoxicity include previous impairment of renal function, histologic diagnosis (FSGS > MCNS), dosage more than 5.5 mg/kg/d, and duration of heavy proteinuria more than 30 days.[162,234] In light of these risks, many pediatric nephrologists perform an initial renal biopsy prior to initiation of cyclosporine, as well as follow-up surveillance biopsies approximately every two years in children requiring long-term cyclosporine use. In summary, while cyclosporine appears to be clinically very helpful for many patients with SRNS, the

long-term risk for cyclosporine nephrotoxicity underscores the importance of efforts to taper and/or transition children to alternate forms of therapy within two years of starting cyclosporine whenever possible.

Mycophenolate mofetil

A few studies have reported the use of MMF in SRNS. In a group of 16 adults with membranous nephropathy, treatment with MMF (500–2000 mg/day) for a mean of 8 months resulted in an approximately 50% reduction in proteinuria in 6 patients (38%) after a mean duration of 6 months.[235] Only 2 patients (12%) had a partial remission, and although total cholesterol was lower, no changes in proteinuria, creatinine, or albumin were seen after MMF treatment. In a 6-month trial of MMF in 18 adults with steroid-resistant FSGS, a notable improvement in proteinuria in 44% of patients by 6 months was found, which was sustained for up to 1-year post-treatment in 50% of this group.[236] No patient had a complete remission, and relapses were common.

Only two reports to date have evaluated the efficacy of MMF in children with SRNS. The first study analyzed the efficacy of MMF + angiotensin blockade for a mean treatment time of 3 years in 9 children and young adults (mean = 14 years; range 6–24 years).[237] Following confirmation of steroid resistance, these authors noted an initial significant reduction in proteinuria (mean urine protein/creatinine ratio from 13 to 8) after 4–8 weekly IV pulses of methylprednisolone, and an even further reduction in proteinuria (mean urine protein:creatinine ratio from 8 to 3.5) within 6 months after starting treatment with MMF (250–500 mg/m^2/day; maximum = 2000 mg/day) + ACEI or ARB therapy. With continued treatment this level of proteinuria (urine protein/creatinine ratio 3.5–4) was maintained for up to 24 months, and was associated with preservation of renal function, improvements in serum albumin, cholesterol and triglycerides, and significant reduction in the number of hospitalizations per year (4.2 to 1.2). The second study evaluated the use of MMF (800–1200 mg/m^2/day) for 12 months in 14 children (mean = 10 years; range 3.5–15 years) with SDNS and SRNS.[175] This study revealed a significant reduction in the mean number of relapses per year (from 2.85 to 1.07) in the overall group between the 12 months preceding and the 12 months following introduction of MMF. Of note, however, within the subset of 5 children who were steroid-resistant and cyclosporine-dependent, there was also a 50% reduction in the number of relapses per year (from 2.8 to 1.4). The above findings in both adults and children suggest that while MMF may have a moderately beneficial role in the management of SRNS, it is not very effective in inducing complete remission in this group of patients, and may thus be most useful as an adjunct to the other alternative therapies.

Tacrolimus

Tacrolimus is among the newer immunosuppressive medications to be used in the setting of SRNS. It is a macrolide antibiotic that was isolated from the fungus *Streptomyces tsukubaensis*. Similar to cyclosporine, it functions via inhibition of calcineurin, leading to inhibition of IL-2 gene transcription in lymphocytes. However, its mechanism of action in nephrotic syndrome is also unknown. Tacrolimus has been used in SRNS since about 1993, when a report in 7 children and adults with this disease noted that tacrolimus monotherapy (i.e. without steroids or other immunosuppressive medications) resulted in induction of complete remission in 3 patients (43%), and partial remission in another 3 patients (43%).[238] Also similar to cyclosporine, withdrawal of therapy resulted in early relapses in 2 patients (28%), both of which responded well to re-introduction of tacrolimus. Although there was relatively little published in this area for the next several years, two very recent reports have again suggested tacrolimus as an effective therapy for this disease. In the first report, six adults with FSGS who were not previously treated with steroids, alkylating agents, or calcineurin inhibitors were prospectively treated with tacrolimus.[239] This resulted in partial remissions (mean = 75% reduction in proteinuria) in all six patients, but no complete remissions. In addition, 5 other adults in stable complete or partial remissions on cyclosporine (± steroids) were converted to tacrolimus. The three in complete remission remained in remission during a mean follow-up of 16 months, while the two in partial remission had a further 47% decrease in proteinuria. The second study is the largest report to date on tacrolimus, and reports the results of tacrolimus treatment combined with tapering doses of prednisone in 16 children with SRNS.[240] After a mean follow-up of 6.5 months (range = 2.5–18 months) these investigators found that 13 children (81%) entered complete remission within an average of 2 months (range = 0.5–5 months), while 2 children (13%) had partial remission, and one (6%) failed to respond. Among the 13 complete responders, 3 children (23%) relapsed while on tacrolimus. Side effects developed among 8 children (50%), and included new or worsening hypertension (5 children), sepsis (1 child), seizure (1 child), and anemia (1 child). The above reports, although representing far fewer children than have been reported for IV methylprednisolone or cyclosporine, suggest that tacrolimus may be as or more effective in SRNS as the other currently available options. It should be kept in mind however, that although none of the reported patients to date have developed diabetes or interstitial fibrosis, no long-term follow-up data have been reported and these are important potential side effects that could dampen enthusiasm for tacrolimus as more experience is gained with long-term follow-up studies.

Plasma exchange and immunoadsorption

Despite continued uncertainty about the pathogenesis of nephrotic syndrome, many reports have suggested that a circulating factor may be responsible for the increased permeability of the glomerular filtration barrier to protein.[32,36,37,241] Based on this, plasma exchange and immunoadsorption have both been attempted for this disease. A retrospective study that included 7 children with SRNS due to FSGS evaluated the efficacy of plasma exchange, with or without subsequent plasma immunoadsorption, who also were receiving simultaneous treatment with a variety of other therapies.[242] The authors

noted that 2 children (29%) entered complete remission, while 2 (29%) entered partial remission, and 3 (43%) failed to respond. Among the complete responders who had subsequent relapses, treatment with plasma immunoadsorption also effectively reduced proteinuria. The authors suggested that the response to this treatment supported the concept that a circulating factor was responsible for proteinuria. Although several other reports have shown dramatic effectiveness of plasma exchange and immunoadsorption in nephrotic syndrome recurring after renal transplantation,[57,58,243,244] it remains unclear if the pathophysiologic mechanism(s) of disease recurrence after transplantation is similar to that occurring in native kidneys. Overall, the use of plasma exchange and immunoadsorption remains limited for management of childhood SRNS.

Azathioprine

The effectiveness of azathioprine in SRNS is controversial. In an early prospective, double-blind placebo-controlled clinical trial in 1970 comparing azathioprine + steroids to steroids alone for nephrotic syndrome in 197 children, the authors identified 31 steroid-resistant patients and determined that 12% of the steroid-resistant children in each group entered full remission, while 13% of each group experienced partial remission.[245] Two other reports[246,247] also did not support a benefit of azathioprine. Thus, azathioprine appears to offer no advantage over several of the other treatments discussed above for the management of children with SRNS.

Levamisole

Levamisole is unique among the treatments for nephrotic syndrome in that it is the only drug used in this setting which has known immunostimulatory, rather than immunosuppressive, effects. Despite this unique attribute, however, like the other medications discussed above, neither levamisole's mechanism of action nor the target cell involved in the response of patients with nephrotic syndrome is known. There have been two uncontrolled trials reporting the use of levamisole in SRNS. The first study included five children with SRNS who had been previously treated with cyclosporine and/or a cytotoxic agent and were subsequently treated with levamisole at a dose of 2.5 mg/kg on alternate days for a mean of 7 months (range = 2–16 months). Although none of these children had side effects, none of them subsequently entered remission.[248] As part of a larger more recent study in 34 children with nephrotic syndrome, the long-term efficacy of levamisole was also evaluated in six additional steroid-resistant children.[249] Treatment with levamisole at a dose of 2 mg/kg daily resulted in significant reductions in both mean proteinuria (1.53 to 0.11 g/day) and cumulative steroid dose (9086 to 1505 mg) during the average 17 month follow-up period. Although side effects were not specifically reported for the steroid-resistant group, reversible neutropenia developed in 5 of 34 children (15%), but no cutaneous, gastrointestinal, or neurological side effects were seen. Potential explanations for the highly discrepant results between these studies might be the differing dosing regimen for levamisole, as well as the prior or simultaneous use of corticosteroids, cyclosporine, and alkylating agents. In comparison to the other agents that have been better-studied in SRNS above, however, levamisole does not appear to offer any distinct clinical advantages in this patient group.

ACE inhibitors

Angiotensin-converting enzyme inhibitors (ACEIs) are being increasingly used in the management of SRNS. The antiproteinuric effect of this class of medication has been attributed to multiple factors, including a decrease in transcapillary hydraulic pressure, a decrease in glomerular capillary plasma flow rate, and alteration in the permselectivity of the glomerular filtration barrier.[251–253]

Several uncontrolled studies involving both children and adults with SRNS have reported significant reductions in proteinuria in response to ACEI.[250–254] In general, the vast majority of patients (70–100%) experienced a reduction in proteinuria. A meta-analysis of 41 adult studies comprising 1124 patients also confirmed that ACEI induced significantly greater reduction in proteinuria compared with equivalent blood pressure reduction from other classes of antihypertensives.[255] One prospective study compared the use of low-dose (0.2 mg/kg/day) and high-dose (0.6 mg/kg/day) enalapril in reduction of proteinuria. They found that high-dose enalapril resulted in a greater median reduction of proteinuria (52%) than low-dose therapy (33%).[257] Another study reported a conversion from non-selective proteinuria to albumin-selective proteinuria during ACEI treatment, suggesting that ACEI may alter permselectivity of the glomerular filtration barrier.[252] Among the side effects noted with ACEI therapy are transient acute renal failure, cough, and hypotension.

Despite the above encouraging results, two recent reports have provided some less enthusiastic support for ACE inhibitors in SRNS. In the first study comparison was made between 12 months of treatment with the ACE inhibitor ramipril and the calcium channel blocker verapamil among 21 adults with steroid-resistant disease.[257] These authors found that while both treatments reduced proteinuria (ramipril = 71%; verapamil = 48%), there was no statistically significant difference in the reduction in proteinuria between the groups. Based on these findings the authors suggested that verapamil may be a reasonable substitute for ramipril in steroid-resistant patients with contraindications to ACE inhibitors. The second study, citing that almost all prior studies of ACE inhibitors had been performed among primarily Caucasian patients, evaluated the efficacy of lisinopril among an entirely African group of 14 children with SRNS.[258] Although the study was severely compromised by the fact that no quantitative data were reported on the reduction in proteinuria, these authors reported that only 2 patients (14%) entered into complete remission in response to lisinopril after 4 and 4.5 months of treatment.

ACE inhibitors may also have important clinical benefits with regard to the hyperlipidemia seen during nephrotic syndrome. A few reports have noted improvement in serum lipid levels in excess of that expected by the improvement in proteinuria and serum albumin levels.[250,251,254] In addition, a recent prospective study in 28 adults with chronic nondiabetic

nephropathies and proteinuria > 2 g/day analyzed the effects of increasing doses of lisinopril on serum lipid abnormalities.[259] These authors found that while proteinuria was significantly reduced even at low doses of lisinopril (10 mg/day), serum lipids (total and LDL cholesterol, triglycerides) progressively decreased in a dose-dependent manner during up-titration of the drug to maximal doses (40 mg/day). Importantly, these benefits were achieved with only modest side effects, which included reversible hypotension in 2 (7%) patients. These findings suggest that, in addition to their anti-proteinuric effects, ACE inhibitors also appear to have beneficial effects on the hyperlipidemia known to complicate SRNS. Since chronic proteinuria and hyperlipidemia are known risk factors for both progressive renal disease and cardiovascular complications,[195–202,260] the combined benefits of ACE inhibitors in reducing both proteinuria and hyperlipidemia provide significant support for their routine use in SRNS.

Antioxidants

Vitamin E is a naturally occurring, lipid-soluble antioxidant which may be of clinical benefit in children with SRNS. The development of nephrotic syndrome has been correlated with an early and transient induction of glomerular reactive oxygen species (ROS),[261] as well as a decrease in glomerular antioxidant enzyme activity.[262] Moreover, patients with nephrotic syndrome have been found to accumulate products of oxidative damage to membranes (lipid peroxides) in the renal cortex,[263] in glomeruli[264,265] and in urine.[263–265] In addition, in animal studies pre-treatment with ROS scavengers[266–268] or the iron chelator deferoxamine (which prevents iron-catalyzed production of ROS)[269] prior to induction of experimental nephrotic syndrome has been shown to markedly attenuate or completely prevent both clinical and histologic disease. Serum levels of the antioxidants vitamin E, vitamin C, and carotene in children with nephrotic syndrome also have been found to be significantly low during relapse, with improvement (but not normalization) during remission, further supporting a correlation between oxidative stress and nephrotic syndrome.[270] In a prospective study, the specific effects of vitamin E (200 IU bid) on proteinuria, serum cholesterol, serum albumin, and GFR were compared between 11 children with nephrotic syndrome due to FSGS (8 of which were steroid-resistant) and 9 children with nephrotic-range proteinuria due to other glomerular and non-glomerular diseases. After a mean of 2.9 months of therapy, the authors found a significant reduction in first-morning urine protein:creatinine ratios in 10 of the 11 children with FSGS (the mean protein:creatinine ratio decreased from 9.7 to 4.1 (58%)), but no reduction in proteinuria among those children with proteinuria due to other causes (the mean protein:creatinine ratio decreased from 2.5 to 2.4). No side effects of vitamin E treatment were noted, and there were no changes in serum cholesterol, albumin, or GFR. Although these limited data do not prove that vitamin E will induce a prolonged anti-proteinuric effect in children with SRNS, evidence of reduction in proteinuria, combined with the absence of reported side effects and a favorable side effect profile of vitamin E, suggest that consideration should be given to the use of vitamin E in these children.

Complications

Infection

Infections represent the most serious complication of nephrotic syndrome. Prior to the development of antibiotics and corticosteroids, serious infections developed in as many as 75% of children with nephrotic syndrome, and the mortality rate was almost 60%.[139] Even in recent years, an estimated 70% of deaths in children with nephrotic syndrome occur due to infection, 50% of which are due to peritonitis.[271]

Because of this increased risk for potentially serious infections in nephrotic syndrome, development of abdominal pain or fever should prompt a careful evaluation for possible peritonitis or other infections. Despite the high risk for infection during nephrotic syndrome, induction of remission generally results in complete normalization of the functional abnormalities in the immune system seen during relapses.[272,273] Since nearly all patients entering remission are also on immunosuppressive medications, however, they remain at somewhat increased risk for infection due to the need for continued use of these medications.

The most common forms of infection seen in nephrotic patients are cellulitis, peritonitis, and sepsis (Table 11.5). Meningitis and pneumonia occur less frequently. Most infections are caused by *Streptococcus pneumoniae*, although infection by Gram-negative organisms such as *Escherichia coli* and *Haemophilus influenzae*, are also commonly seen. The basis for the increased risk of infection among these patients is multifactorial, and likely results from both disease-related and treatment-related issues as shown in Table 11.5. Patients with nephrotic syndrome are known to have functional abnormalities in their immune system. These abnormalities include low serum IgG levels, due to urinary loss of IgG, without an apparent compensatory increase in IgG synthesis, and abnormal function of T lymphocytes.[274] In addition, decreased levels of factors B (C3 proactivator) and D, both components of the alternative complement pathway, result in a decreased ability to opsonize encapsulated bacteria such as *S. pneumoniae*. Induction of remission generally results in complete normalization of the functional abnormalities in the immune system and reduces the risk of infections in these patients.[275]

The incidence of spontaneous peritonitis is about 5% in children with nephrotic syndrome.[276] This condition is believed to develop in the setting of ascites, which is a good culture medium. Peritonitis usually occurs in patients in relapse and with ascites, and manifests with fever, abdominal pain and tenderness, and leukocytosis.[277] The diagnosis of peritonitis in a child with nephrotic syndrome may be more difficult while being treated with corticosteroids. However, Krensky et al noted that treatment with corticosteroids did not mask clinical

Table 11.5 Risk factors and clinical presentation of infections in nephrotic syndrome

Risk factors	Clinical presentation
Low IgG levels	Cellulitis (most often due to *Staphylococcus*)
Impaired T-lymphocyte function	Peritonitis (most often due to *Pneumococcus*)
Impaired tissue perfusion due to edema	Sepsis
Low factor B (C3 proactivator) levels (decreased bacterial opsonization)	
Low factor D levels (decreased bacterial opsonization)	
Immunosuppression due to corticosteroids	
Immunosuppression due to other agents	

manifestations of spontaneous peritonitis in nephrotic children.[277] The laboratory evaluation of a child with suspected peritonitis is usually notable for leukocytosis with a neutrophil predominance. If the diagnosis is suspected, a paracentesis should be performed to allow peritoneal fluid to be analyzed for WBC count and sent for culture. Clinical features of peritonitis accompanied by a peritoneal white blood cell count greater than 250/mm^3 are considered diagnostic of peritonitis.[278,279] *S. pneumoniae* and *E. coli* are the most common pathogens in peritonitis, but other pathogens have been reported.[276,280,281] Initial treatment of peritonitis should consist of IV broad-spectrum antibiotics. The antibiotic choice can be narrowed after culture results are available. Gram stains have been shown to be misleading and should not be relied upon for antibiotic decision making. Negative cultures can occur if the bacterial load is low. It has therefore been recommended that blood culture bottles be used as a medium to increase the diagnostic yield.[282]

Some patients with nephrotic syndrome experience recurrent episodes of peritonitis, suggesting a specific host risk factor. In one study, levels of IgG were significantly lower in nephrotic syndrome patients with peritonitis when compared to age-matched controls with nephrotic syndrome in relapse.[276] In addition, a recent case-controlled series of children with nephrotic syndrome with and without peritonitis found that patients with a serum albumin ≤1.5 gm/dl at initial presentation had a 9.8 fold higher likelihood of developing peritonitis.[278]

Prevention of peritonitis includes two approaches: immunization against potential pathogens and prophylactic antibiotics. Immunization against *Pneumococcus* is recommended, and has been shown to be more effective in patients with steroid sensitive nephrotic syndrome who are in remission.[283] Vaccination against *Pneumococcus* has also been shown to be efficacious even when children with nephrotic syndrome are on steroids.[284] However, a recent study also found that patients with SSNS immunized with a polyvalent Pneumoccoccal vaccine had a reduction in anti-Pneumoccoccal antibodies when followed for up to 36 months.[285]

The 2000 American Academy of Pediatrics statement on the use of heptavalent conjugated Pneumococcal vaccine recommended universal vaccination of all children up to 23 months old, while those children 24–59 months of age have been recommended to only receive this vaccine if they are deemed at moderate to high-risk, including patients with nephrotic syndrome.[286,287] It is hoped that the frequency of Pneumococcal infections will decrease in susceptible individuals, as has been recently shown in very young children (≤24 months old).[288]

The use of prophylactic antibiotics is somewhat more controversial. Although a recent review on this subject supported its use, especially in high-risk patients (age <2 years, steroid-resistant and frequent relapsing patients, children with a previous Pneumococcal infection),[289] others have noted that prophylactic antibiotic usage may result in development of resistant organisms.[290]

Development of edema itself during nephrotic syndrome can also increase the risk for infection. As edema develops, the increased hydrostatic pressure in the interstitium can lead to reduced perfusion of the interstitium. This can predispose edematous patients to the development of skin breakdown, and potential development of cellulitis.[275]

Viral infections also can be serious for patients with nephrotic syndrome who are taking corticosteroids or other immunosuppressive medications. Varicella represents the most serious potential infection, and immunization or documentation of varicella immunity is important in children with nephrotic syndrome to minimize the risk for development of potential life-threatening disseminated varicella infection.

Acute renal failure

Acute renal failure (ARF) is another complication of nephrotic syndrome that occurs in a small percentage of children. This reduction in renal function is usually transient, but case reports of profound renal involvement exist in the literature. There are reports of children requiring dialysis for short periods, and in rare instances extensive periods, before resolving.[291] Possible explanations for this include: renal vein thrombosis, reduced renal perfusion, acute tubular necrosis, interstitial edema within the renal parenchymal bed, and alterations in glomerular permeability. A recent report of 11 children with biopsy-proven MCNS with oliguric ARF found that alterations in glomerular permeability played a greater role than that of reduced renal perfusion in these patients.[292]

Thromboembolism

Thromboembolism is a potentially life-threatening complication of nephrotic syndrome. The incidence of thromboembolism in children has been reported to range from 1.8 to 5%,[194,294–296] with the incidence being twice as high among children with SRNS as compared with SSNS.[194] In adults, especially those with membranous nephropathy, the cumulative incidence of thrombosis reaches nearly 40–50%.[297,298] It is possible that this complication is underestimated in children due to subclinical manifestations. In one study of 26 children with SSNS who were systematically evaluated by ventilation–perfusion scans to look for pulmonary emboli, findings consistent with pulmonary embolism were reported in 28% of children.[298]

The majority of episodes of thrombosis in children are venous in origin, although arterial thrombosis has been reported in 19–45% of cases.[193,293] The most common sites for thrombosis are the deep leg veins, inferior vena cava, and ileofemoral veins, although a variety of other veins and arteries have been reported to be affected[193,293,299] (Table 11.6). In addition, central venous catheters, which are sometimes used in the management of patients with refractory nephrotic syndrome with poor vascular access, can further increase the risk of thrombosis.

Pain and swelling of an extremity is suggestive of a deep venous thrombosis, and upper extremity swelling accompanied by neck and facial swelling in the setting of a central venous catheter should raise clinical suspicions for a central venous thrombosis. Similarly, development of acute renal failure or gross hematuria should prompt a renal Doppler ultrasonographic evaluation for possible renal vein or inferior vena cava thrombosis. Finally, development of respiratory distress or cardiovascular symptoms should prompt evaluation by chest X-ray and consideration of a ventilation–perfusion or chest CT scan to exclude possible pulmonary embolus.[300,301]

This complication can be life threatening and has resulted in some reported deaths in the pediatric age group.[302] Reports in adults have also implicated the concomitant use of diuretics as a possible aggravating factor for patients who are already in a hypercoagulable state.[303]

Although no single laboratory abnormality can reliably predict thrombosis in these patients, a number of risk factors for thrombosis are present in most patients with nephrotic syndrome (Table 11.6). Intravascular volume depletion during nephrotic syndrome can result in increased blood viscosity. This hyperviscous state can be further increased iatrogenically if diuretics are not used very judiciously in patients with nephrosis. Importantly, in the largest pediatric study to date furosemide was found to be the major iatrogenic risk factor for thrombosis, having been used in 78% of cases of thrombosis (7 of 9 children).[193] Increased platelet aggregation and/or thrombocytosis can also increase the risk for thrombosis. Increased procoagulant factors (Factors I, II, V, VII, VIII, X, and XIII) and fibrinogen levels are thought to occur as a result of increased hepatic synthesis.[271,304] Decreased coagulation inhibitors such as antithrombin III are also usually seen, due to urinary losses, and appear to correlate with the degree of hypoalbuminemia.[274,275] Although low-dose aspirin has been used in some cases to try to compensate for this abnormality, particularly in patients in whom thrombosis has already occurred, no controlled trial has yet demonstrated the efficacy of aspirin in reducing the risk for thrombosis. Alterations in the fibrinolytic system (decreased plasminogen and increased α2-antiplasmin), hyperlipidemia, and altered endothelial cell function have also been reported to increase the risk for thrombosis.[25,295,304] The role of the coagulation inhibitors, protein C and protein S, in the risk for thrombosis is somewhat controversial. Urinary loss of these low molecular weight coagulation inhibitors, in combination with increases in the high molecular weight protein C and protein S binding proteins (due to increased hepatic synthesis), have been suggested to lead to reduced levels of free (biologically active) protein C and protein S, and to thus also contribute to the increased risk for thrombosis.[274] However, this concept is inconsistent with a report of increased serum levels of protein C antigen and its anticoagulant activity, as well as increased total and free protein S levels, in patients with nephrotic syndrome compared to a control group.[305] When anticoagulant factors are lost in the urine, the venous radicles draining the kidney are a prime location for the development of renal vein thrombosis, as this is a site

Table 11.6 Risk factors and clinical presentation of thromboembolism in nephrotic syndrome

Risk factors	Clinical presentation
Intravascular volume depletion (results in increased blood viscosity) Increased platelet aggregation (sometimes also thrombocytosis) Increased procoagulatory cofactors (factors I, II, V, VII, VIII, X, and XIII) Decreased coagulation inhibitors (antithrombin III) Fibrinolytic system alterations (decreased plasminogen, increased α_2-antiplasmin) Increased fibrinogen levels (results in increased blood viscosity) Decreased zymogen factors (factor IX, factor XI) Altered endothelial cell function Hyperlipidemia	Deep venous thrombosis Inferior vena cava thrombosis Renal vein/artery thrombosis Pulmonary vein/artery thrombosis Pulmonary embolus Peripheral vein/artery thrombosis Cerebral venous thrombosis (sagittal sinus)

where anticoagulant concentrations would be minimal, while hemoconcentration would be maximal, increasing the risk for thrombosis. It should be noted that these coagulation abnormalities tend to correlate with disease severity, in that almost all of them normalize once remission can be induced.

Respiratory distress

In some patients, initiation of an albumin infusion in the setting of anasarca can lead to the development of acute respiratory distress. Most often this is a result of rapid return of interstitial fluid to the intravascular space, resulting in development of pulmonary edema. High-risk patients include those with severe edema, those receiving albumin without adequate diuretics, and those with compromised renal function. However, other causes for respiratory distress, such as pleural effusion and pulmonary thromboembolism, should also be considered in any child with nephrotic syndrome who develops tachypnea or hypoxia. In the clinical setting of pleural effusion with respiratory compromise, hospitalization for monitoring and diuresis (often with albumin) is usually necessary. As noted above, in the setting of systematic screening of asymptomatic children with nephrotic syndrome using ventilation perfusion scans, 28% of children had findings consistent with pulmonary embolism.[298]

Cardiovascular disease

Cardiovascular disease is increasingly recognized as an important complication of nephrotic syndrome in patients who require long-term treatment. Recognized cardiovascular risk factors include hyperlipidemia, hypertension, long-term exposure to corticosteroids or other immunosuppressive agents which can alter serum lipid levels, hypercoagulability, and oxidant stress.[295] This complication has been well recognized in adults, where patients with nephrotic syndrome were found to have a relative risk of myocardial infarction of 5.5 and a relative risk of coronary death of 2.8 compared to a control group.[202]

Hyperlipidemia consisting of increased cholesterol and triglycerides is a consistent feature in nephrotic syndrome. In general, hyperlipidemia tends to improve when patients achieve remission, making children with SSNS at low risk of sustained hyperlipidemia. On the other hand, children with SRNS can develop total cholesterol levels > 700 mg/dL. In addition to elevated total cholesterol, low density lipoprotein (LDL) cholesterol and very low density lipoproteins (VLDL) cholesterol are consistently elevated in nephrotic syndrome.[306] High density lipoprotein (HDL) cholesterol levels, on the other hand, vary from low to high.

Treatment of hyperlipidemia with the use of atorvastatin has been reported to induce a 41% reduction in LDL cholesterol, a 31% reduction in triglycerides, and a 15% increase in HDL cholesterol.[307] In addition, chronically nephrotic adults treated with HMG CoA reductase inhibitors (statins) have been reported to have improvements not only in their lipid profiles, but also in their endothelial dysfunction, creatinine clearance, proteinuria, and serum albumin levels compared to non-statin treated control patients.[308,309] In contrast, however, similar treatment for chronically nephrotic children has not yet been demonstrated in a controlled trial to be both safe and beneficial, and was recently reported to be routinely used by only 31% of pediatric nephrologists for the management of refractory nephrotic syndrome.[178] Despite this lack of proof in children, however, the evidence accumulated in adults suggests that serious consideration should be given to initiation of HMG-CoA reductase inhibitors in children with persistent nephrotic syndrome and demonstrated high lipid levels.

Anemia

Chronic nephrotic syndrome can also lead to the development of anemia. This is thought to be due primarily to the loss of both erythropoietin and transferrin into the urine. These losses, in combination with a reduced serum half-life for erythropoietin, and increased transferrin catabolism, can result in the development of an erythropoietin-responsive anemia or iron deficiency in patients who remain chronically nephrotic.[310,311] Although treatable with erythropoietin, induction of remission of the nephrotic syndrome is the most effective approach to correct the anemia.

Endocrine abnormalities

Loss of multiple binding proteins for hormones into the urine during nephrotic syndrome can result in various endocrinologic abnormalities. Because vitamin D-binding protein, largely complexed with 25-hydroxycholecalciferol is lost in the urine during nephrotic syndrome, patients can sometimes develop low serum levels especially when unremitting nephrosis is present.[275] Perhaps not surprisingly, low levels of 1,25-dihydroxycholecalciferol D3 have been reported in nephrotic syndrome; which is explainable by ongoing losses of its substrate (25, OH D3) in the urine. Modest hyperparathyroidism has also been noted in nephrotic syndrome as well.[275,312] Vitamin D supplementation in nephrotic syndrome is usually reserved for patients with unremitting nephrosis, or those who develop chronic kidney disease, secondary hyperparathyroidism, or persistent significant hypocalcemia.[313]

Binding proteins for corticosteroid and thyroxine (T_4) are also lost into the urine during nephrotic syndrome. Decreased levels of total 17-hydroxycorticosteroid have been noted, but patients also have an increased percentage of free cortisol, resulting in the absence of any clinical cortisol deficiency.[275] Similarly, although occasional low levels of total T_4 and triiodothyronine T_3 are seen, free T_4 and thyroid-stimulating hormone (TSH) levels are typically normal, and clinical hypothyroidism is not considered to be present.[8] Thus, despite losses of both of these binding proteins into the urine during nephrotic syndrome, clinical abnormalities resulting from these losses appear not to occur. The exception to this, though is congenital nephrotic syndrome where hypothyroidism can be

severe, and supplementation of infants with levothyroxine is commonly done to avoid the risks of hypothyroidism on neurodevelopmental well being.[314,315]

Deficiencies of both copper and zinc have also been reported in nephrotic syndrome. Decreased serum copper levels have been attributed to loss of ceruloplasmin in the urine, while decreased zinc levels have been attributed to loss of zinc into the urine attached to albumin, its main binding protein.[275] The potential clinical relevance of zinc deficiency to nephrotic syndrome relates to its possible role in the immunologic abnormalities and growth impairment that have been associated with nephrotic syndrome, although this role is as yet unproven.

Treatment-related side effects

In addition to complications resulting from nephrotic syndrome, a number of side effects can also result directly or indirectly from the treatment of the disease.

Corticosteroids

Compared to children with SSNS, children with SDNS or FRNS are at increased risk for steroid-induced side effects. In addition, patients with SRNS in whom long-term alternate day steroids are continued are also at significant risk for these side effects. Although a detailed discussion of all of the side effects of steroids is beyond the scope of this chapter, some of the more common side effects, including growth impairment, bone demineralization, cataracts, and avascular necrosis of bone are discussed below.

Growth impairment

Although all children with nephrotic syndrome treated with corticosteroids are at risk for decreased linear growth, this is usually only clinically significant in children with FRNS, SDNS, and SRNS (if steroids are continued). Rees et al. reported linear growth delay in boys and girls with SSNS, with a negative height deviation score correlating with the duration of steroid use in boys.[316] These male children were also found to have delayed onset of secondary sexual characteristics and blunted pulsatile release of growth hormone and gonadotropins. The authors concluded that one explanation for linear growth impairment with corticosteroids was a delayed onset of puberty. Further support for the detrimental effects of corticosteroids on linear growth was provided by Padilla and Brem, who demonstrated an increase in linear growth rates from 4.3 cm/year to 8.7 cm/year in preadolescent children with FRNS and SDNS who were treated with alkylating agents in conjunction with a reduction in steroid dosing.[317] More recently, a comprehensive study of long-term linear growth in severe SSNS was performed by Emma et al.[318] These authors found that prepubertal linear growth and final adult height were adversely affected, and that the pubertal growth spurt was delayed in males, but not in females. Diagnosis of nephrotic syndrome before 3.5 years of age was associated with a much greater negative effect on prepubertal linear growth. These younger patients experienced more relapses and received prednisone for a greater length of time and at a higher cumulative dose when compared to those diagnosed after 3.5 years of age. Prednisone treatment was the only variable found to correlate with a negative height deviation score, while other variables such as relapse rate or steroid sparing regimen did not alter growth independent of their association with prednisone dosing. Importantly, recovery of growth was seen when steroid withdrawal occurred prior to the onset of puberty.

The association of alternate day steroids with growth impairment is somewhat more controversial. Polito et al. found that the use of alternate day corticosteroids in nephrotic syndrome did not adversely affect linear growth or bone maturation (as assessed by bone age measurements).[319] In contrast, Emma et al. did see growth impairment in children on alternate day steroids, but primarily in those patients with severe disease and a high cumulative dose of corticosteroids.[318] In general, transition to alternate day dosing of steroids, preferably in the morning, is preferable to try to minimize the risks of steroid-induced growth impairment.

Bone demineralization

Prolonged use of corticosteroids is well known to have significant effects on bone mineralization. Corticosteroids cause increased bone resorption: they act on bone by stimulating osteoclast activity. More importantly, they also decrease bone formation by reducing osteoblast number and function.[320] In a recent study, however, the bone mineral content was not found to be significantly different from controls.[321] This was attributed in part to the increased body mass index (BMI) of steroid-treated patients, since high BMI is associated with an increased bone density. Despite many previous concerns, it appears that the obesity risk resulting from corticosteroids may be at least somewhat protective with regard to the risk of decreasing bone mineral content.[321]

Cataracts

Posterior capsular cataracts are the most common ocular abnormality seen in children with nephrotic syndrome. They have recently been reported to occur in 3 of 29 (10.3%) children with nephrotic syndrome treated with corticosteroids.[322] Among those children with cataracts, nephrotic syndrome had been diagnosed significantly earlier (2 years vs. 5.4 years), and the authors suggested that those children diagnosed with nephrotic syndrome earlier may be at increased risk for the development of steroid-induced cataracts. It should be noted, however, that cataracts in this setting do not usually result in loss of visual acuity.[323] In general, children with nephrotic syndrome treated with corticosteroids should be screened for cataracts using an ophthalmoscope at each clinic visit. Practically speaking, the eyes should be systematically scanned by adjusting the diopter settings to look for any charcoal gray or black defects located in the posterior chambers of the eyes. If cataracts are seen, children should be referred to an ophthalmologist to document the size of the cataracts and allow close follow-up of this complication.

Avascular necrosis of the femoral head

Corticosteroid use also increases the risk of avascular necrosis of the femoral head. The basis for this has been suggested by an animal study using piglets that found that methylprednisolone reduced the blood flow to the femoral head, which may be an early risk factor for the development of osteonecrosis.[324] Although the overall incidence of this side effect in children with nephrotic syndrome does not appear to be high, it should always be considered in the differential diagnosis of a child with nephrotic syndrome and previous or current corticosteroid usage that develops hip pain, knee pain, or an alteration of gait that is otherwise unexplained.

Alkylating agents

Alkylating agents used in nephrotic syndrome can induce a number of side effects of which the clinician should be aware and attempt to prevent. Hemorrhagic cystitis is a serious side effect of cyclophosphamide which appears to be decreasing in frequency due to efforts designed to prevent it. A recent meta-analysis estimated its incidence at 2.2% among children with FRNS.[156] This side effect develops when acrolein, a toxic metabolite of cyclophosphamide that causes chemical irritation of the transitional epithelium of the bladder, is exposed to the bladder for prolonged periods. The risk for this can be minimized by aggressive hydration in association with either IV or oral cyclophosphamide. Thus, oral cyclophosphamide is usually administered in the morning with aggressive fluid intake throughout the morning and encouragement for children to void at least every 3–4 hours to prevent accumulation of acrolein within the bladder. Other side effects which may be seen during treatment with cyclophosphamide include an increased risk of infections, leukopenia, nausea, thinning of hair, dose-related oligo- or azoospermia, and an increased risk for malignancies (lymphomas and bladder cancer).

Chlorambucil is another alkylating agent which has been used somewhat less frequently than cyclophosphamide for children with nephrotic syndrome. Like cyclophosphamide, chlorambucil use has been associated with an increased risk of infections and malignancies, but infections appear to be more frequent with chlorambucil (6.8% vs. 1.5%).[156] Other reported side effects included seizures (3.4%; not seen with cyclophosphamide) and leukopenia (33%; same as for cyclophosphamide), although the hemorrhagic cystitis that can be seen with cyclophosphamide has not been seen with chlorambucil.

Mycophenolate mofetil

Mycophenolate mofetil has become increasingly popular for the management of FRNS, SDNS, and cyclosporine-dependent nephrotic syndrome. Although gastrointestinal side effects (vomiting/diarrhea) have occurred often when this drug is used for renal transplantation, they have not occurred in a large number of children when used for the treatment of nephrotic syndrome. Baga et al studied 19 children with nephrotic syndrome treated with MMF and reported only occasional abdominal pain in one-fourth of the patients, whereas none experienced vomiting or diarrhea.[176] In another report, 2 of 10 children with nephrotic syndrome experienced gastrointestinal intolerance that was attributed to MMF.[175] Dose-dependent leukopenia is another well known potential side effect of MMF, but this has not been a major reported problem, and can usually be managed with manipulation of the dose, rather than discontinuation of the drug.

Drug-induced hypertension

Clinically significant elevation of blood pressure requiring antihypertensive medications is unusual in children with the nephrotic syndrome in the untreated state. However, treatment with medications such as corticosteroids and calcineurin inhibitors can result in hypertension. Steroids are thought to increase the vascular sensitivity to endogenous vasoconstrictors (angiotensin II and catecholamines) and also to have some modest mineralocorticoid activity, which can result in retention of sodium and water. Cyclosporine appears to increase the systemic vascular resistance through a number of mechanisms, including vasoconstriction due to the effects of endothelin 1, angiotensin II, loss of vasodilating prostglandins and nitric oxide, and increased intracellular calcium.

Antihypertensive agents used to treat drug-induced hypertension usually consist of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers if the patient is clinically stable, or a calcium channel blocker if the patient is not yet hemodynamically stable with regard to intravascular volume. Because patients with SRNS may still have anasarca with low intravascular volume at the time that drug-induced hypertension is recognized, however, clinicians should use caution when initiating ACE inhibitors or angiotensin II receptor blockers in this setting, due to the potential for inducing ARF and/or serious electrolyte abnormalities.

Drug-induced hyperlipidemia

Both cyclosporine and prednisone have been reported in the transplant literature to independently contribute to post-transplant hypercholesterolemia.[325] In one study, further delineation of the effects of each of these medications after transplant was determined by analysis of monotherapy treatment arms. These investigators found that only the patient group weaned from prednisone and maintained on cyclosporine experienced elevations of triglycerides and lipoprotein A levels, and a fall in HDL cholesterol, suggesting that cyclosporine was the main contributor to these patients' hyperlipidemia.[326] Despite this, clarifying the effects of these agents in children with unremitting nephrotic syndrome can be difficult. Montané et al. utilized a steroid-sparing protocol that included initial IV pulse steroids that were tapered to low dose prednisone (20 mg/m^2 on alternate days) or discontinuation, combined with MMF and angiotensin blockade for nine children with SRNS. Although no control group was included, these investigators noted a 50% reduction in both cholesterol and triglyceride levels among patients

converted to this low-dose steroid protocol.[237] Despite these encouraging results, the relative contributions of the minimization of steroids and the presence of MMF and angiotensin blockade could not be addressed in this study. Regardless of the relative contributions of the disease or its treatment to the hyperlipidemia seen in children with persistent nephrotic syndrome, however, treatment of the hyperlipidemia is increasingly being recognized as an important aspect of the overall management of these children.

Calcineurin inhibitor-related side effects

Cyclosporine has proven to be very effective in the treatment of SRNS. However, this medication has several known potential side effects, including gingival hyperplasia, hirsutism, increased risk of infections, hypertension, and hyperkalemia. Toxicity of the central nervous system, including fine tremor, anxiety, headache, peripheral neuropathy, and seizures has also recently been reported with the use of cyclosporine for SRNS, although the pathogenesis of this toxicity is unknown.[327] Perhaps of greatest concern, long-term use of cyclosporine is also associated with an increased risk for development of irreversible renal interstitial fibrosis (cyclosporine nephrotoxicity). In light of the above concerns, alternatives to cyclosporine have recently emerged. Mycophenolate mofetil has recently been reported to be effective at maintaining remission while cyclosporine is stopped, and this transition was reported to be associated with a 56% increase in the mean measured glomerular filtration rate.[328] Concerns about cyclosporine nephrotoxicity will almost certainly stimulate additional efforts to find non-nephrotoxic approaches to induce and/or maintain remission among children with cyclosporine-dependent nephrotic syndrome.

Tacrolimus is another calcineurin inhibitor which is becoming a more popular alternative to cyclosporine for steroid-resistant and cyclosporine-resistant nephrotic syndrome. The side effects reported with this agent in nephrotic children have included increased risk of infections, hypertension, and possibly increased risk of seizures and anemia.[240] Although it is similar to cyclosporine with regard to calcineurin inhibition, tacrolimus appears to differ from cyclosporine primarily in that it appears to induce less gingival hypertrophy, but has a well known risk for inducing new onset diabetes mellitus.

Prognosis

Likelihood of achieving remission

It is generally accepted that the initial response to corticosteroids (i.e. induction of complete remission) is the single best indicator of the long-term prognosis for a child presenting with nephrotic syndrome, as children who fail to respond to an 8 week course of oral corticosteroids have a guarded prognosis. Steroid response has been reported to correlate with renal biopsy findings if done at disease outset prior to the institution of treatment (as was the clinical practice in the early 1970s). In these early studies, while overall steroid responsiveness was seen in 78% of newly-diagnosed children treated with corticosteroids, the likelihood of achieving remission varied greatly by histologic diagnosis.[5] Steroid responsiveness was 93% for MCNS, 30% for FSGS, 56% for mesangial proliferative glomerulonephritis, 7% for MPGN, and 0% for membranous nephropathy.[5] In addition, the likelihood of steroid responsiveness was decreased in older children, possibly related to the increasing incidence of the steroid-resistant glomerulopathies in later childhood. This was supported by the findings that the median ages for clinical presentation with MCNS, FSGS, and MPGN were 3 years, 6 years and 10 years old, respectively.[12]

In contrast, it has historically been much more difficult to induce complete remission among children with SRNS. In 1990 Mendoza et al. reported a complete remission rate of 52% in a group of 23 children with steroid-resistant FSGS.[210] A subsequent larger series from the same center revealed a 66% complete remission rate using a triple therapy protocol of pulse methylprednisolone infusion, oral alternate day corticosteroids, and an alkylating agent.[211] More recently, a response rate of 60–78% has been reported for SRNS treated with cyclosporine.[226,329] Even more recently, 81% of a group of 16 children with treatment-resistant nephrotic syndrome entered complete remission induced by tacrolimus, including a small number of patients who failed to respond to oral corticosteroids, the triple therapy protocol of pulse IV methylprednisolone + alternate day oral corticosteroids + oral cyclophosphamide, and cyclosporine.[240] Given these available therapies, a mathematical calculation encompassing all of the current therapies available for nephrotic syndrome would suggest that the likelihood of any child presenting with nephrotic syndrome never achieving a remission has become very small. This is based on an estimated 78% overall response rate to corticosteroids, an estimated 60% response rate to cyclosporine for SRNS, an estimated 66% response rate to the triple therapy protocol of IV methylprednisolone + alternate day prednisone + alkylating agents, and an estimated 80% response rate to tacrolimus for SRNS and cyclosporine-resistant nephrotic syndrome. Despite these encouraging statistics, however, there remain many children with nephrotic syndrome who have proven unresponsive to all therapies attempted, and these children remain at extremely high-risk for progression to ESRD.

Relapse rate

Relapses of nephrotic syndrome occur commonly in SSNS. Only 30% patients with SSNS will never experience a relapse, although the overall tendency to relapse decreases with time. A large study of MCNS found that there was a gradual tendency toward an increase in the number of non-relapsing patients over time, reaching 80% eight years after onset of disease.[22] Moreover, 75% of those patients who remained relapse-free for the initial six months after treatment either continued in remission during their entire course or relapsed only rarely. Such findings suggest that while the majority of children (60%) with nephrotic syndrome experience one or

more relapses, most patients experience a gradual decrease in the frequency of relapses over time.

ESRD and transplant recurrence risk

Non-responsiveness to corticosteroids clearly identifies those patients at high risk for progressive kidney disease. In one large study of 389 children with nephrotic syndrome, 21% of children with biopsy-proven MCNS who were unresponsive to the initial 8-week course of steroids subsequently progressed to ESRD.[22] Among children with nephrotic syndrome due to FSGS who progress to ESRD, renal transplantation can also pose serious challenges. Nephrotic syndrome recurs in the allograft in approximately 30% of such cases, and results in graft loss in approximately one-half of those patients affected.[330] Because FSGS is the most common glomerulopathy associated with ESRD in children, this matter has received much attention in the pediatric transplantation literature.[331] Disease recurrence can be a devastating complication, and efforts are ongoing to attempt to characterize patients at risk for disease recurrence. Clinical and biopsy features of children at high risk for recurrence of FSGS are: those who reached ESRD within 3–4 years following diagnosis, those with histologic features of mesangial proliferation, and those with previous history of recurrence.[73, 332, 333] Treatment strategies for recurrent nephrotic syndrome post-transplant have included plasma exchange, cyclophosphamide, and intravenous cyclosporine[330,334] but none of these have proven to be uniformly effective.

Mutations of the NPHS2 gene encoding the podocyte protein podocin have been associated with SRNS and a high rate of progression to ESRD.[50] Some have suggested a low risk for recurrence for this form of SRNS.[335,336] However NPHS2 mutations have also been associated with recurrence of proteinuria following transplantation.[337,338] Given this uncertainty, any child with ESRD due to SRNS identified to have a mutation in podocin should be observed carefully for potential recurrence after renal transplantation.

Mortality risk

Since the introduction of antibiotics and corticosteroids several decades ago, and the further refinement of immunosuppressive agents in recent years, the mortality rate for nephrotic syndrome has been reduced to <5% from 67% seen in the preantibiotic era. In a large ISKDC series reported in 1984, the mortality rate was only 1.9%.[339] Importantly, 9 of the 10 deaths in this study occurred in children who either had SRNS or in those who relapsed within the first 8 weeks of steroid therapy, and six of these children died of infections, emphasizing the continued importance of this complication of nephrotic syndrome. Thus, despite dramatic improvements in the mortality risk for children with nephrotic syndrome over the last 50 years, it should be remembered that children who prove to be steroid-resistant remain at increased risk for potentially life-threatening complications of either nephrotic syndrome or its treatment.

Concluding remarks

Nephrotic syndrome is among the most common forms of kidney disease seen in children. It continues to be a fascinating and challenging problem for pediatric nephrologists, as neither the pathogenesis nor the mechanism of action of the drugs which have proven effective in treating it have yet been fully defined. Despite this, unless children with nephrotic syndrome develop resistance to corticosteroid therapy the long-term prognosis is generally excellent. SRNS continues to present significant challenges to pediatric nephrologists, however, since many such children remain unresponsive to even the newest and most effective therapies that have been attempted, leaving them at increased risk for both ESRD and death. Further research on both the pathogenesis and the mechanism of action of effective therapies for nephrotic syndrome is needed to permit the development of more effective and less-toxic therapies for this very common childhood kidney disease.

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12 Inherited nephropathies

Patrick Niaudet

The number of renal diseases that may have a genetic basis is growing. With the expanding knowledge of the human genome, it is becoming easier to identify the genetic defects that may cause disease. Technologic innovations in genetic research have further fueled these efforts. This chapter discusses recent advances and our current understanding of some of the common inherited renal diseases and addresses aspects of their clinical management.

Alport syndrome

Alport syndrome (AS) is an inherited glomerular disease characterized by familial occurrence of a progressive hematuric nephropathy associated with sensorineural hearing loss and characteristic ultrastructural changes of the glomerular basement membrane.[1]

Molecular structure of the glomerular basement membrane

AS is caused by defects in the synthesis of type IV collagen in the glomerular basement membrane (GBM) and other tissues. Type IV collagen molecules have a complex structure consisting of three α chains that form trimers through the association between their NC1 domain at the carboxy-terminal domain. Each α chain has a short 7S domain at N-terminal, a long collagenous domain, and a non-collagenous domain, the NC1 domain, at the C-terminal. The collagenous domain of the α chains folds in triple helices. The triple helices of type IV collagen form a network through several intermolecular interactions, resulting in a non-fibrillar structure (Figure 12.1).

There are six different α chains, named α_1 through α_6. The α_1 and α_2 chains are encoded by COL4A1 and COL4A2 genes located head to head on chromosome 13q34. The α_3 and α_4 chains are encoded by COL4A3 and COL4A4 genes located head to head on chromosome 2q35-37, whereas the α_5 and α_6 chains are encoded by COL4A5 and COL4A6 located head to head on chromosome Xq22.

The expression of the different α chains of type IV collagen can be studied by immunofluorescence, using monoclonal antibodies. The α_1 and α_2 chains are widely distributed in all basement membranes. The α_3, α_4 and α_5 are expressed in the GBM, the Bowman capsule, the distal and collecting duct basement membrane and basement membranes in the cochlea and in the eye. In addition, the α_5 chain, contrary to the α_3

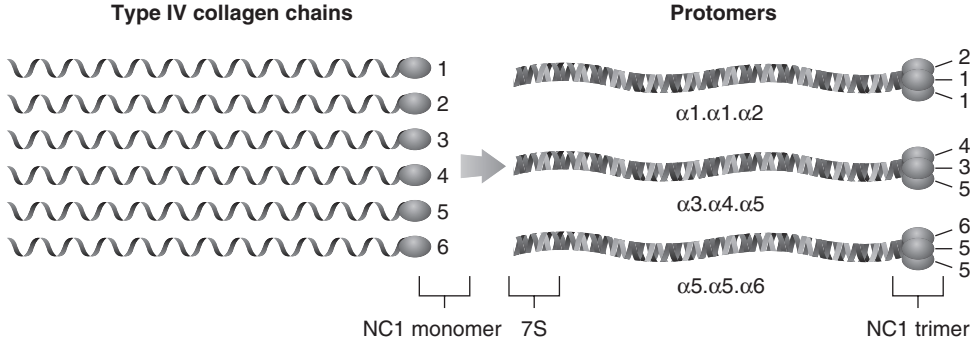

Figure 12.1 Triple helical organization of the type IV collagen family. Six genetically distinct α chains are arranged into three triple helical protomers that differ in their chain composition. Each protomer has a 7S triple helical domain at the N-terminal; a long, triple helical, collagenous domain in the middle of the molecule; and a non-collagenous (NC1) trimer at the C-terminal. Interruptions in the Gly–Xaa–Yaa amino acid sequence at multiple sites along the collagenous domain (white rings) confers flexibility, allowing for looping and supercoiling of protomers into networks. The selection of α chains for association into trimeric protomers is governed by molecular recognition sequences encoded within the hypervariable regions of NC1 domains. (Reproduced from N Engl J Med 348: 2543, 2003, with permission from Massachusetts Medical Society.)

and the α_4 chains, is expressed in the epidermal basement membrane (Table 12.1).

Genetics

X-linked Alport syndrome

Alport syndrome is genetically heterogeneous with X-linked, autosomal recessive and autosomal dominant forms. In approximately 85% of patients, Alport syndrome is inherited as an X-linked disease and is due to mutations in the COL4A5 gene encoding the α_5 chain of collagen IV (Table 12.2). More than 200 mutations affecting COL4A5 gene have been identified.[2] Identification of more than 80% of these mutations can be done using polymerase chain reaction (PCR) and direct sequencing of exons. Genetic testing in the diagnosis of AS is generally restricted at the present time to prenatal diagnosis, exclusion of carrier state in an asymptomatic female, or when the diagnosis is not possible with renal and skin biopsies. De-novo mutations occur in 10% of cases.[3,4]

Autosomal recessive Alport syndrome

The autosomal recessive form of AS is observed in approximately 15% of patients. Both females and males with this type of AS have a severe disease, similar to the course of males with X-linked AS. The mutations in these patients affect COL4A3 or COL4A4 genes, located on chromosome 2q35-37.[5] The autosomal dominant form of AS is very rare and is due to mutations in COL4A3 or COL4A4 genes. Patients have a clinical course similar to males with X-linked AS, although the rate of progression is slower.[6,7]

Clinical manifestations

Renal disease

Renal disease in AS is characterized by hematuria, which is a constant feature in males with X-linked AS and in both sexes in autosomal recessive AS. Microscopic hematuria is present early in life. Episodes of macroscopic hematuria are often observed following upper respiratory tract infections in young children. Females with X-linked AS may have intermittent hematuria and a few of them may never have hematuria.

Proteinuria often develops several years later in males with X-linked AS, and in both males and females with autosomal recessive AS. It increases progressively with time, and may result in nephrotic syndrome. Mild proteinuria is less frequent or may be intermittent in females with X-linked AS.

Table 12.1 Distribution of α3, α4 and α5 chains of type IV collagen chains in renal basement membranes (BMs) seen in Alport Syndrome

	Glomerular BM	Bowman capsule	Collecting duct BM	Epidermal BM
Normal:				
α_3/α_4	+	+	+	–
α_5	+	+	+	+
X-linked males:				
α_3/α_4	–	–	–	–
α_5	–	–	–	–
X-linked females:				
α_3/α_4	Mosaic			–
α_5	Mosaic			Mosaic
Autosomal recessive:				
α_3/α_4	–	–	–	–
α_5	–	+	+	+

Table 12.2 Molecular genetics of Alport syndrome (AS)

	Defective chain	Locus	Chromosome
X-linked AS with sensorineural hearing loss	α_5	COL4A5	Xq22
X-linked AS with leiomyomatosis	α_5 and α_6	COL4A5 and COL4A6	Xq22
Autosomal recessive AS	α_3 α_4	COL4A3 COL4A4	2q35-q37 2q35-q37
Autosomal dominant AS	α_3 or α_4	COL4A3 or COL4A4	2q35-q37

Hypertension also develops with advancing disease in males with X-linked AS as well as in autosomal recessive AS.

Chronic kidney disease (CKD) develops in all affected males with X-linked disease, with some differences in the rate of progression between families.[8] In some families, affected males progress to end-stage renal disease (ESRD) in late teens or early 20s, and the rate of progression in these families is often similar in the affected males. In other families, progression to ESRD occurs later (around 40 years of age), and the rate of progression varies between individuals in the same family. CKD develops during the second or third decade of life in males and females with the autosomal recessive variant of AS.[9] Females with X-linked AS have a better prognosis, most of them have a mild disease, and usually they do not develop CKD.[10]

Hearing defect

Sensorineural hearing loss is the most common extrarenal manifestation in AS.[11] It is not present at birth and can be demonstrated by audiometric examination in 85% of boys and 18% of girls before the age of 15 years. The defect initially consists of a reduction in sensitivity to tones within the 2000–8000 Hz range. Hearing loss is progressive and later affects conversational frequencies. Clinically significant hearing deficit is present by late childhood or adolescence. Progression of hearing loss often parallels the progression of renal disease, and is always seen in the presence of significant renal disease. Hearing loss is often mild in females with X-linked AS, but there is no difference in the degree of hearing deficit between males and females with autosomal recessive AS.

Ocular anomalies

Ocular lesions are observed in X-linked AS and autosomal recessive AS. Anterior lenticonus is a conical protrusion of the lens in the anterior chamber, which develops progressively and is seen mainly in males (Figure 12.2).[9] The lesion is bilateral in three-quarters of patients, and is considered pathognomonic of AS. Lenticonus may be accompanied by lens opacities and reduction of visual acuity. Retinal lesions are asymptomatic and consist of pigmentary changes of the perimacular area, with granulations around the foveal area. These lesions are always present in cases with lenticonus, but may occur in its absence. Corneal lesions consisting of posterior polymorphic dystrophy or recurrent corneal ulcerations have also been reported.

Renal pathology

There are no characteristic findings seen in AS by light microscopy, and renal biopsy is often normal in young children. Later in life, capillary walls may be thickened and irregular. Increased mesangial matrix and segmental sclerosis also develops, along with tubulointerstitial lesions. Lipid-laden foam cells are often seen in the interstitium of advanced AS (Figure 12.3). Immunofluorescence studies may show C3 granular deposits.

The expression of type IV collagen α chains in the kidney and in the skin may be diagnostic.[1] In most males with X-linked AS, there is no staining of the GBM, Bowman capsule, and tubular basement membrane (TBM) for α_3, α_4, and α_5 (IV) chains, whereas in female patients the expression of these chains is irregular, especially in the GBM. Skin biopsy may be diagnostically useful in some patients, obviating the need for a renal biopsy. The lack of expression of α_5 (IV) in the epidermal basement membrane in a male patient with X-linked AS is diagnostic, but a normal expression is observed in approximately 20% of cases. In female patients, with X-linked AS, α_5 (IV) expression is often irregular but a normal expression does not exclude the diagnosis of the disease or a carrier state.

In male and female patients with autosomal recessive AS, α_3 and α_4 (IV) chains are not expressed in the GBM, Bowman capsule, and the distal TBM, whereas α_5 (IV) is expressed in Bowman capsule and distal TBM but not in the GBM. In these patients, expression of α_5 (IV) in the skin is normal.

The characteristic lesion observed in electron microscopy consists of an irregular thickening of the GBM, with splitting of the lamina densa and microgranulations (Figure 12.4). In

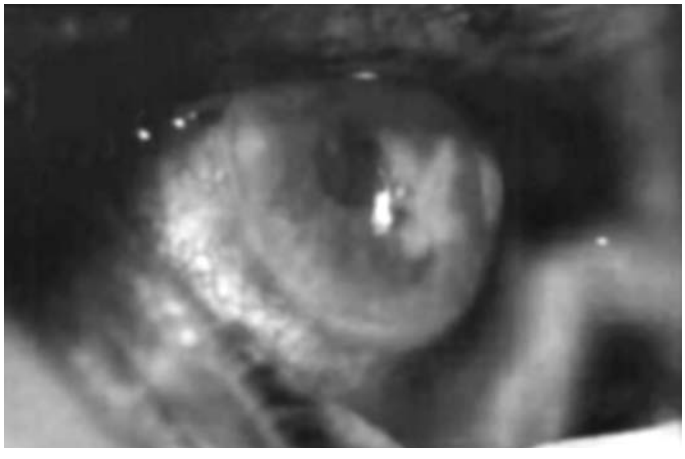

Figure 12.2 Lenticonus in Alport syndrome.

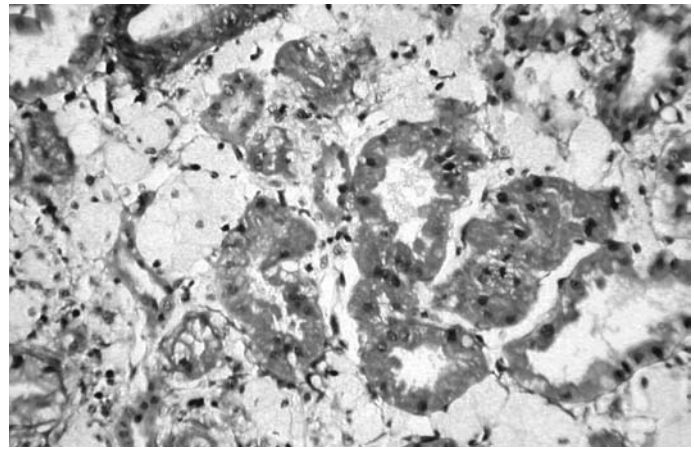

Figure 12.3 Light microscopy of a patient with Alport syndrome demonstrating foam cells distributed within the interstrtium.

children, thickening of the GBM is often segmental. These characteristic lesions may be absent in some patients with AS, and the GBM may appear normal or uniformly thin.

Leiomyomatosis

The association of esophageal, tracheobronchial, or genital leiomyomatosis and X-linked AS have been reported in more than 30 families. Esophageal lesions are responsible for dysphagia and retrosternal pain and are recognized by radiologic investigations. Tracheobronchitis may cause dyspnea, recurrent pulmonary infections, and complications during anesthesia. Affected females may have vulvar and clitoral enlargement. Leiomyomatosis with AS is due to deletions removing the 5′ end of both the COL4A5 and COL4A6 genes (Alport contiguous gene syndrome). The deletion involves only the first two exons (exons 1 and 2) of COL4A6 but its extent is variable in the COL4A5 gene.[12]

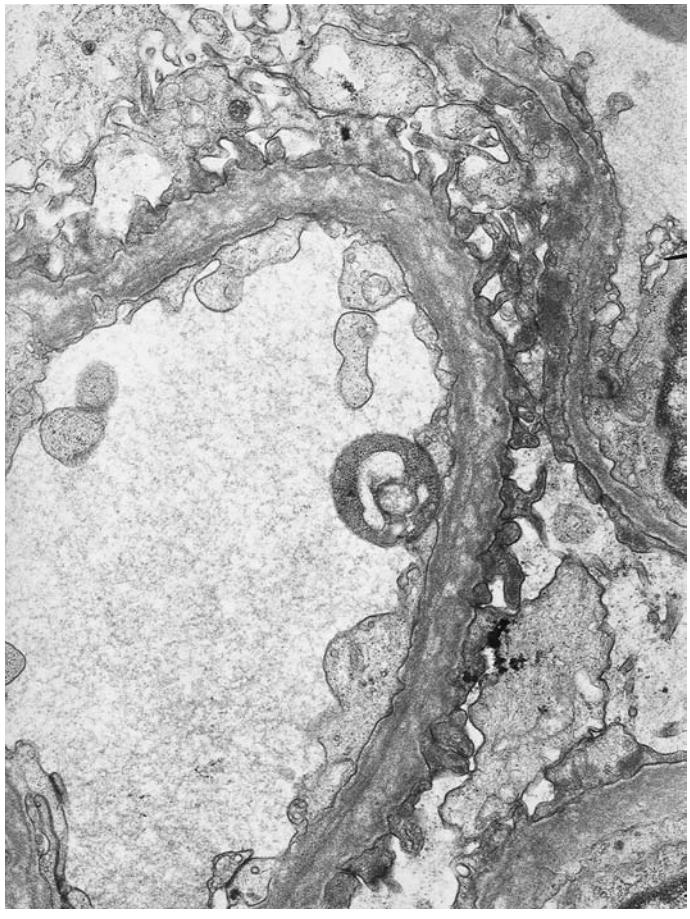

Figure 12.4 Electron photomicrograph showing the abnormalities of glomerular basement membrane (GBM) in Alport syndrome. The GBM is thickened and the lamina densa is split, giving it a 'moth-eaten' appearance. Effacement of podocyte foot processes is evident.

Thin basement membrane nephropathy (benign familial hematuria)

Thin basement membrane nephropathy or benign familial hematuria (BFH) is characterized by asymptomatic microscopic hematuria and sometimes episodes of macroscopic hematuria. Renal biopsy shows a diffuse thinning of the GBM (< 200 nm). Patients rarely develop proteinuria or hypertension, and renal function usually remains normal.

BFH is a familial disorder, with an autosomal dominant mode of inheritance. The underlying genetic defect is likely to be a heterozygous mutation of COL4A3 or COL4A4 genes.[13] Indeed, heterozygous carriers of COL4A3 or COL4A4 mutations in AS families frequently have asymptomatic microscopic hematuria and thin GBM by electron microscopy. Several investigators have found mutations in the COL4A3/COL4A4 genes in a high proportion of families with BFH, which confirms that most cases of thin basement membrane nephropathy represent a heterozygous state of autosomal recessive AS.[13,14] However, other disorders with different molecular anomalies may be associated with thin basement membrane nephropathy. Although the long-term prognosis is excellent in the majority of patients, some patients have been reported to progress to renal failure in association with the development of proteinuria and histologic lesions of focal segmental glomerulonephrosis (FSGS).[15]

Epstein syndrome and Fechtner syndrome

Some patients with autosomal dominant hereditary nephritis and sensorineural deafness also show thrombocytopenia with giant platelets, an association referred to as Epstein syndrome. Patients with Fechtner syndrome have, in addition, leukocyte cytoplasmic (Döhle-like) inclusions (Figure 12.5). These two syndromes were thought to be related to AS until it was recently shown that these patients had mutations in MYH9, a gene on chromosome 22 which encodes non-muscle myosin heavy chain 9.[16,17] Non-muscle myosins are hexadimeric proteins with ATPase activity. MYH9 is expressed in the kidney, the cochlea, the platelets, and leukocytes. MYH9 mutations cause Epstein syndrome, Flechtner syndrome, May–Hegglin anomaly (macrothrombocytopenia and leukocyte inclusions),

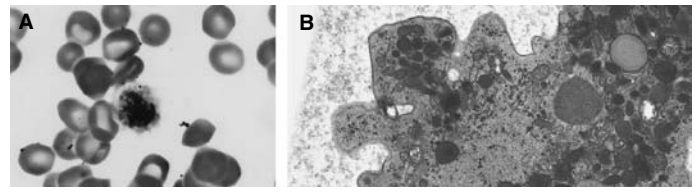

Figure 12.5 Fechtner syndrome. (A) Peripheral smear showing enlarged ('giant') platelets. The platelets are slightly larger than the adjacent red blood cells. (B) Electron micrograph of a neutrophil showing characteristic cytoplasmic inclusions. (Reproduced with permission from Pediatr Nephrol 13:782, 1999.)

Sebastien syndrome (macrothrombocytopenia and leukocytes inclusions different from the May–Hegglin anomaly), and autosomal dominant deafness (DFNA).[18] Since MYH9 mutations are found in only 74% of the patients, genetic heterogeneity may be present in the remainder of patients.

Management

There is no specific treatment for Alport's syndrome. There is evidence that angiotensin-converting enzyme (ACE) inhibitors may reduce proteinuria and slow the progression to renal failure.[19,20] In one study from Spain, cyclosporine was shown to reduce proteinuria and delay the progression to ESRD.[21] Hearing loss should be detected early in order to provide hearing aids, which may prevent further degradation.

Either hemodialysis or peritoneal dialysis may be proposed as treatment for ESRD and does not raise specific problems in patients with AS. Renal transplantation results in patients with AS are similar to patients with other diseases. Anti-GBM nephritis develops in 3–4% of patients, usually during the first year. These patients develop anti-GBM antibodies and transplant biopsy often shows crescentic glomerulonephritis.[22,23] The anti-GBM antibodies are often directed against the NC1 domain of the α_5 chain of type IV collagen.[24] It is believed that patients develop antibodies against antigens present on the donor GBM for which the donor has not acquired immune tolerance. Treatment with plasma exchanges and cyclophosphamide has little effect on allograft outcome.

Finnish-type congenital nephrotic syndrome

Congenital nephrotic syndrome of the Finnish type (Finnish CNS) is an autosomal recessive disease that is more frequent in the Finnish population, with an incidence of 1/10 000 newborns,[25] whereas it is considerably less frequent in other countries.

Genetics

The abnormal gene of Finnish CNS has been localized to the long arm of chromosome 19 in both Finnish and non-Finnish families.[26,27] There is no genetic heterogeneity of the disease. The gene, called NPHS1, contains 29 exons. It encodes a 1241 amino acid transmembrane protein, named nephrin, which is a member of the immunoglobulin superfamily of cell adhesion molecules and is phosphorylated by Src family kinases.[28] Nephrin is located at the slit diaphragm of the glomerular podocytes.

Four different mutations in this gene were found to segregate with the disorder in affected Finnish families. The two most common mutations, Fin-major and Fin-minor, account for nearly 90% of all affected Finnish patients.[28] Fin-major is a 2 bp deletion in exon 2, whereas Fin-minor is a nonsense mutation in exon 26: these mutations are detected in 78% and 16% of Finnish patient's alleles, respectively. More than 50 other mutations in the nephrin gene have been discovered in patients elsewhere around the world.[29,30]

Clinical features

Finnish CNS is characterized by massive proteinuria, starting in utero. A large placenta (placentomegaly), weighing more than 25% of the birth weight (Table 12.3), is common and most infants are born prematurely. Edema may be present at birth or appears within the first weeks of life. Massive proteinuria is accompanied by hypoalbuminemia, often less than 1 g/dl (10 g/L). Other proteins such as immunoglobulin G, transferrin, antithrombin III, ceruloplasmin, vitamin D, and thyroxine-binding proteins are also lost in the urine. The plasma concentrations of these proteins are low and serum cholesterol and triglycerides are markedly increased.[31]

Table 12.3 Characteristics of Finnish-type congenital nephrotic syndrome (CNS) and diffuse mesangial sclerosis

	Finnish-type CNS	Diffuse mesangial sclerosis
Onset of proteinuria	Antenatal	At birth, more commonly in the first year of life
Alpha-fetoprotein in amniotic fluid	Always increased	Usually normal
Placenta	>25% birth weight	Usually normal
Proteinuria	Massive (>20 g/L with hypoalbuminemia < 15g/L)	Usually less severe
Renal function	Normal during the first year	Renal failure within few months after discovery
Histology	Dilatations of proximal tubules	Mesangial sclerosis
Genetics	NPHS1 gene mutations	WT1 gene mutations in Denys–Drash syndrome and some cases of isolated diffuse mesangial sclerosis

Urinary protein losses and poor food intake lead to severe malnutrition and poor linear growth. These children are highly susceptible to bacterial infections, including peritonitis, cellulitis, and respiratory infections. Thromboembolic complications occur due to the severity of the nephrotic syndrome. Hypothyroidism is also common.

Renal ultrasonography shows enlarged, hyperechogenic kidneys with a loss of normal corticomedullary differentiation. Plasma creatinine is initially normal but later increases, and ESRD usually occurs between 3 and 8 years of age.

There are no pathognomonic microscopic features in renal biopsy. Irregular dilation of the proximal convoluted tubules is the most characteristic finding (Figure 12.6), whereas mild mesangial hypercellularity and increased mesangial matrix are observed in the glomeruli (Figure 12.7).[32] Glomerulosclerosis, interstitial fibrosis, lymphocytic and plasma cell infiltration, tubular atrophy, and periglomerular fibrosis develop later in the course of the disease. Interstitial changes usually parallel the degree of glomerulosclerosis.

Management

The nephrotic syndrome in Finnish CNS is always resistant to corticosteroids and immunosuppressive drugs. Furthermore, these drugs may be harmful, due to the already high susceptibility to infection. Conservative treatment includes daily or every other day albumin infusion, γ-globulin replacement, maintaining nutrition with a high-protein, low-salt diet, vitamin and thyroxine substitution, and prevention of infections and thrombotic complications.[33]

Providing adequate nutrition may require nasogastric tube feeding, or parenteral alimentation. The rate of intercurrent complications remains high, and growth and development are usually retarded.

A combination of an ACE inhibitor and indomethacin therapy may lead to a marked decrease in protein excretion and improvement in nutritional status and growth.[34,35] Nevertheless, some patients may require bilateral nephrectomy to prevent continued massive protein losses before the development of renal failure. If nephrectomy is performed, dialysis is provided until the patient reaches a weight of 8–9 kg. At this stage, renal transplantation can be considered.[33] Proteinuria can develop in the graft. This has been reported in 25% of children in Finland who had the Fin-major/Fin-major genotype, which is associated with the absence of nephrin in the native kidneys. Antibodies directed against nephrin may be found in these patients.[36]

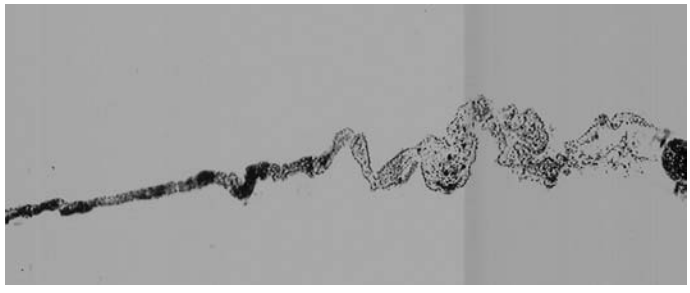

Figure 12.6 Finnish-type congenital nephrotic syndrome. Microdissection of a nephron showing a cyst in the proximal tubule.

Antenatal diagnosis

Finnish CNS can be diagnosed prenatally by demonstrating high levels of α-fetoprotein (AFP) in the amniotic fluid and maternal serum. This test has been used in high-risk families at 15–16 weeks of gestation.[37] However, high AFP levels in the amniotic fluid are not specific for Finnish CNS, and elevated maternal serum AFP levels are less reliable. Moreover, fetuses heterozygous for NPHP1 mutations may have elevated AFP levels, leading to false diagnosis.[38] The localization of the NPHP1 gene and its identification allow a definitive prenatal diagnosis from chorionic villous sample analysis, either by linkage analysis in informative families or by direct genetic testing when the mutation has been identified in an affected sibling, can lead to a definitive prenatal diagnosis.

Nephrotic syndrome and podocin mutations

Using a positional cloning approach, Boute et al identified a new gene, NPHS2, associated with an autosomal recessive form of nephrotic syndrome characterized by an early onset, steroid resistance, rapid progression to renal failure, and the absence of recurrence after transplantation.[39] NPHS2 is only expressed in podocytes and encodes a 383-amino acid integral membrane protein, podocin. By immunoelectron microscopy, podocin is located at the foot processes and is expressed exclusively at the slit diaphragm.[40] This 42 kDa protein is structurally related to human stomatin, an adapter protein which links mechanosensitive channels to the cytoskeleton on the cell surface. Podocin has been shown to interact with CD2AP and nephrin in the slit diaphragm. Podocin directs the targeting of nephrin to lipid rafts.[41]

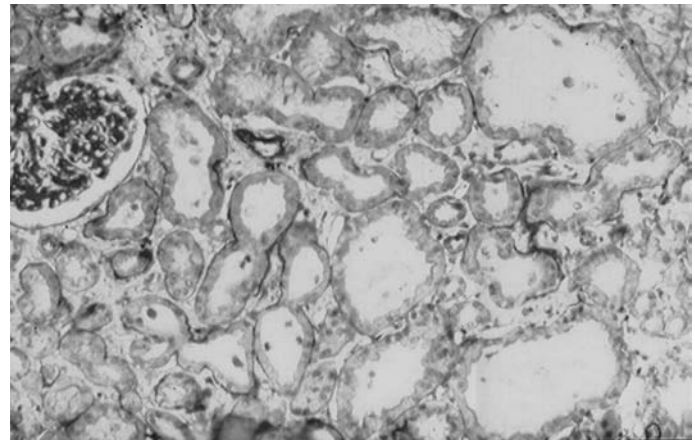

Figure 12.7 Light microscopy of renal biopsy in Finnish-type congenital nephrotic syndrome. Mild mesangial proliferation and dilated proximal tubules are the prominent features.

NPHS2 mutations were first described in familial autosomal recessive steroid-resistant idiopathic nephrotic syndrome with FSGS. Podocin mutations account for approximately 40% of families with autosomal recessive FSGS.[42] It was later shown that mutations of NPHS2 may also occur in patients with late-onset FSGS.[43] Ten different NPHS2 mutations, comprising nonsense, frameshift, and missense mutations, were found to segregate with the disease. Podocin mutations have been identified in 15–30% of patients with the sporadic form of steroid-resistant idiopathic nephrotic syndrome.[42–46]

A few patients with congenital nephrotic syndrome were found to lack NPHS1 mutations. In some of them, homozygous NPHS2 mutations were identified.[47] In addition, some patients have both NPHS1 and NPHS2 mutations, resulting in a tri-allelic abnormality (homozygous mutations in one gene and a heterozygous mutation in the other).[47,48]

Denys–Drash syndrome

The association of diffuse mesangial sclerosis, male pseudohermaphroditism, and Wilms' tumor characterizes Denys–Drash syndrome (DDS).[49,50] Affected infants develop proteinuria and nephrotic syndrome with rapid progression to ESRD. Some children have an incomplete form of the syndrome, with diffuse mesangial sclerosis associated with male pseudohermaphroditism or Wilms' tumor.

Genetics

The Wilms' tumor suppressor gene (WT1) encodes a transcription factor presumed to regulate the expression of numerous target genes through DNA binding (Figure 12.8).[51,52] It plays a key role in kidney and gonadal maturation, and when mutated, results in the occurrence of nephroblastoma and/or glomerular diseases (Denys–Drash syndrome and Frasier syndome). The WT1 gene contains 10 exons, covering approximately 50 kB of genomic DNA. Exons 1–6 encode a proline/glutamine-rich transcriptional regulatory region, whereas exons 7–10 encode the four zinc fingers of the DNA-binding domain. Two alternative splicing regions, one corresponding to the 17 amino acids encoded by exon 5 and the other to three amino acids (lysine–threonine–serine (KTS)) encoded by the 3′ end of exon 9, lead to the synthesis of four isoforms with definite and stable proportions, and different functions. The target genes potentially regulated by WT1, usually negatively, include genes coding for transcription factors and for growth factors or their receptors.

WT1 is strongly expressed during embryo–fetal life. In the mature kidney, WT1 expression persists only in podocytes and epithelial cells of Bowman capsule. WT1 gene disruption in mice results in the absence of kidneys and gonads, suggesting a key role of WT1 in the maturation of the genito-urinary tract.

DDS is often a sporadic disorder, and the majority of patients have constitutional mutations of the WT1 gene.[53–55] More than 80 germline de-novo mutations have been identified in patients with complete or incomplete DDS. Most are missense mutations located within exon 8 and 9, which encode zinc fingers 2 and 3. These mutations result in alterations in the DNA-binding capacity of the WT1 protein.

Clinical manifestations

Children with DDS appear normal at birth, with a normal birth weight and without placental enlargement. The nephrotic

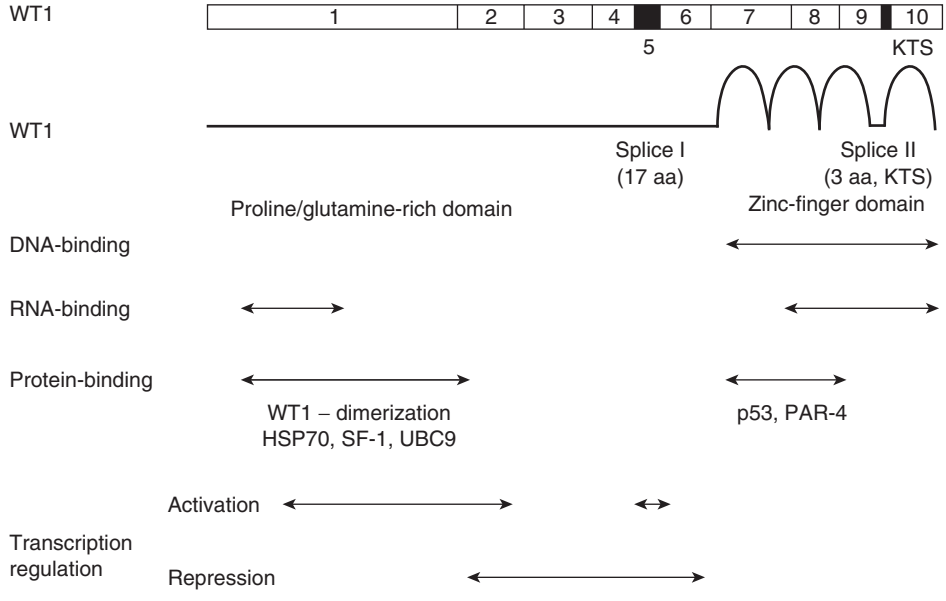

Figure 12.8 Structure of the WT1 mRNA and protein.

syndrome may be present at birth. More often, proteinuria develops postnatally, increasing progressively during the first or the second year of life with nephrotic syndrome. Arterial hypertension is frequent. All children progress to ESRD. This usually occurs before age 3 years, often within a few months after the discovery of renal symptoms.[56]

Wims' tumor may be the first manifestation of the syndrome. The tumor may be unilateral or bilateral, and is associated in a few cases with nodules of nephroblastomatosis. Male pseudohermaphroditism, characterized by ambiguous genitalia or female phenotype with dysgenetic testis or streak gonads, is observed in all 46 XY patients. In contrast, all 46 XX children appear to have a normal female phenotype.

Pathology

The typical glomerular lesion observed in DDS consists of diffuse mesangial sclerosis (Figure 12.9). It is characterized in the early stages by a fibrillar increase in mesangial matrix, without mesangial cell proliferation.[57] The capillary walls are lined by hypertrophied podocytes. The fully developed lesion consists of a combination of thickening of the glomerular basement membranes and massive enlargement of mesangial areas, leading to reduction of the capillary lumens. The mesangial sclerosis eventually contracts the glomerular tuft into a sclerotic mass within a dilated urinary space. There is usually a corticomedullary gradient of involvement, with the deepest glomeruli being less affected. Tubules are severely damaged.

Management

The nephrotic syndrome in DDS is resistant to corticosteroids and immunosuppressive drugs. Treatment is supportive and consists of maintenance of electrolyte and water balance, maintaining adequate nutrition, prevention and treatment of infectious complications, and management of renal failure. Bilateral nephrectomy should be performed at this stage because of the risk of developing a Wilms' tumor. Recurrent disease does not develop in the transplant.

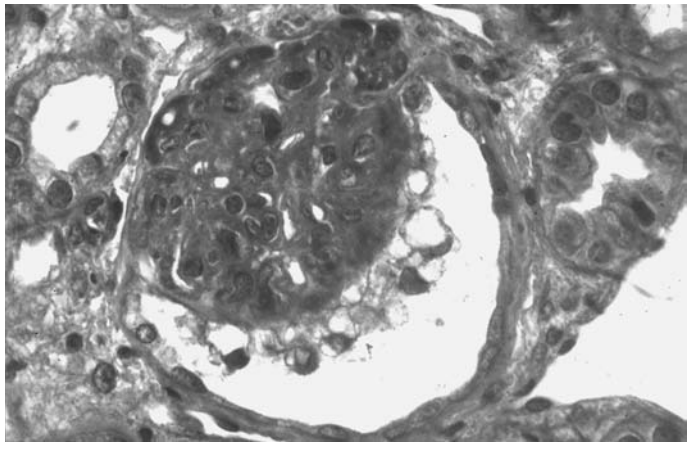

Figure 12.9 Light microscopy in diffuse mesangial sclerosis. Glomerulus showing contracted glomerular tuft that is surrounded by enlarged podocytes.

Frasier syndrome

Frasier syndrome is characterized by male pseudohermaphroditism and progressive glomerulopathy, usually with FSGS.[58,59] Proteinuria is detected in childhood, generally between 2 and 6 years of age, increases progressively with age, and does not respond to any treatment. The disease slowly progresses to ESRD. Patients have female external genitalia. Often, the disorder is diagnosed during the evaluation of primary amenorrhea in females with nephrotic syndrome, which leads to the diagnosis of 46 XY gonadal dysgenesis, at the origin frequently of gonadoblastoma. No recurrence of the nephrotic syndrome is observed after renal transplantation.

Frasier syndrome is caused by mutations in the donor splice site in intron 9, which results in the loss of the +KTS isoform of WT1. Semiquantitative RT-PCR (reverse transcriptase polymerase chain reaction) analysis of the +KTS/–KTS transcripts isolated from patient lymphocytes indicates a significant reduction in the +KTS transcripts compared with normal controls.[60,61]

The classical definition of Frasier syndrome includes 46 XY patients with a female phenotype. However, similar WT1 mutations may be responsible for the occurrence of isolated persistent glomerulopathy, with FSGS, in genetically female patients.[62,63] Transmission of the mutation is possible. Systematic research for WT1 intronic mutation should be carried out to know precisely the incidence of WT1 intronic mutations in patients presenting with 'idiopathic' steroid-resistant proteinuria/nephrotic syndrome progressing to renal failure.

Nail–patella syndrome

The nail-patella syndrome (NPS) or osteo-onychodysplasia is an autosomal dominant disease characterized by hypoplastic or absent patella, dystrophic fingernails and toenails, and dysplasia of elbows and iliac horns.[64,65] Renal involvement is inconstant. The estimated incidence of NPS is 22 per million population. The disease has been reported in patients worldwide.

Extrarenal manifestations

Nail abnormalities are present in 80–90% of patients with NPS, and are observed at birth.[66] The nails may be absent but, more often, are hypoplastic or dysplastic. Abnormalities predominate on the fingernails, particularly the thumb and index finger, whereas the toenails are often normal (Figure 12.10). The following lesions in the nails are present bilaterally and symmetrically: discoloration, longitudinal pterygium, splitting, and triangular lunulae.[67]

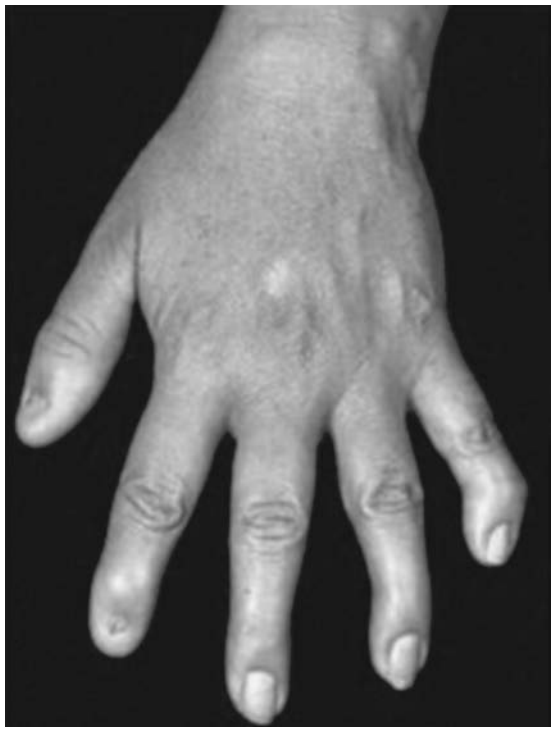

Figure 12.10 Photograph of hand in nail-patella syndrome showing dysplasia of the nails. The severity of dysplasia decreases from the thumb to the fifth finger. Clinodactyly of the fifth finger and triangular lunulae are also present.

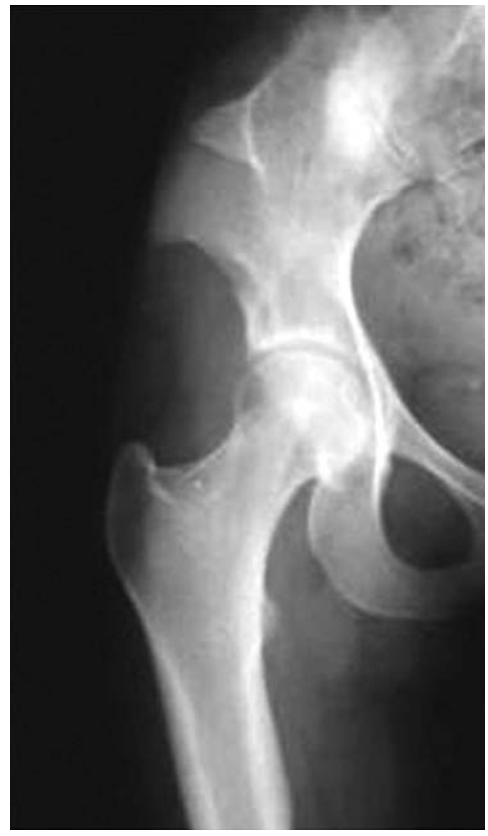

Figure 12.11 X-ray of the hip and iliac bones showing iliac horn in a patient with nail-patella syndrome.

Abnormalities of the knees and elbows are found in almost all patients.[68] The patella may be absent or hypoplastic, often with fragmentation, causing lateral slippage during knee flexion. Complications such as arthritis, arthrosis, and knee effusion may lead to knee pain.

Elbow symptoms are also commonly seen. The radial heads are typically hypoplastic, leading to subluxation. The distal ends of the humerus are also hypoplastic and posterior processes result in limitations of extension, pronation, and supination of the forearm. Iliac horns (Figure 12.11), observed in 30–70% of the patients, are pathognomonic radiologic features of the disease. They consist of asymptomatic symmetrical bone formations arising from the antero-superior iliac crest. Other bone anomalies that affect the feet and the ankles may be seen as well as scoliosis.

Renal manifestations

Renal disease is present in approximately 50% of the patients with the NPS.[69] Females and males are equally affected. The degree of renal involvement varies between families and also within members of the same family. The most frequent symptoms are proteinuria, sometimes with the nephrotic syndrome, hematuria, and hypertension.[70] Urine-concentrating ability may be impaired.

ESRD develops in approximately 30% of cases at a mean age of 33 ± 18 years.[66] The evolution of the renal disease is extremely variable, suggesting that non-genetic factors may be involved in the rapid deterioration of renal function observed in some patients.

Light microscopy examination of the renal biopsy shows normal, or nearly normal, glomeruli in patients with normal renal function. In comparison, patients with heavy proteinuria and/or impaired renal function may show basement membrane thickening and non-specific lesions of FSGS. Immunofluorescence microscopy is either negative, or shows non-specific segmental deposits of IgM and C3 in the sclerotic areas. Electron microscopy shows pathognomonic and consistent lesions of the GBM.[71,72] These lesions consist of irregular and lucent rarefactions within the lamina densa, containing clusters of cross-banded collagen fibrils. These abnormalities may also be found in the mesangial matrix, but the tubular basement membranes are not affected. Immunohistochemical studies have shown an irregular mesangiocapillary localization of type III collagen and an abnormal distribution of type VI collagen.

Genetics

The abnormal gene in NPS is located at the distal end of the long arm of chromosome 9. A transcription factor of the LIM-homeodomain type, which plays an important role for

limb development in vertebrates, named LMX1B, was mapped to the same location at 9q34. A large number of mutations in this gene have been identified in patients with NPS;[73,74] these defects are believed to result in the loss of function of this protein. LMX1B is expressed in the podocyte. The study of homozygous knockout mice has shown that this gene regulates the transcription of four genes, COL4A3, COL4A4, CD2AP, and NPHS2.[75,76]

It has been suggested that there may be two allelic mutations of the gene: one responsible for the NPS without nephropathy and one responsible for the NPS with nephropathy. It has been calculated that, for a parent with the NPS whose family has nephropathy, the risk of having a child with nephropathy is 24% and the risk of having a child who will progress to ESRD is 7%.[77]

Management

There is no specific therapy available in NPS and symptomatic therapy for chronic renal failure needs to be instituted. Renal transplantation can be offered as the renal replacement therapy for ESRD. The GBM lesions do not recur after renal transplantation.

Nephronophthisis

Nephronophthisis, initially described in 1951 by Fanconi, is a chronic tubulointerstitial nephritis which uniformly progresses to ESRD.[78] Nephronophthisis is an autosomal recessive disorder and accounts for 5–10% of cases of ESRD in children. Nephronophthisis is part of the nephronophthisis-medullary cystic kidney disease complex. These disorders share a number of common clinical features as well as a triad of histologic characteristics: tubular basement membrane disintegration, tubular cyst formation, and tubulointerstitial inflammation and fibrosis.[79,80] Nephronophthisis has three clinical variants: juvenile nephronophthisis, infantile nephronophthisis, and adolescent nephronophthisis. Of these, juvenile nephronophthisis is the most common and well characterized.

Juvenile nephronophthisis

The first symptoms generally develop after the age of 2 years. Polyuria with polydipsia are common and are due to poor urinary concentrating ability. These symptoms become more pronounced after the age of 4 years. Decreased urinary concentrating defect is demonstrated by a low urinary osmolarity (<400 mOsm/L), which does not increase after DDAVP (desmopressin) administration. Urinary sodium wasting may be responsible for hyponatremia and hypovolemia, if sodium intake is diminished. Decreased growth velocity results in growth retardation. Hematuria and proteinuria are absent or minimal. Blood pressure is normal before the onset of ESRD.

Later symptoms are related to progressive renal insufficiency and include anemia, metabolic acidosis, and other manifestations of uremia, such as nausea, anorexia, and weakness. ESRD develops at a mean age of about 13 years.

Diagnosis

Renal ultrasound may be normal, with normal-sized kidneys, but renal parenchymal hyperechogenicity and loss of corticomedullary differentiation is often observed. At later stages, small cysts are present in the medulla. There is no dilatation of the urinary tract. The diagnosis of nephronophthisis should be considered if a child presents with polyuria, urinary sodium loss, growth failure, renal insufficiency without hematuria or proteinuria, normal blood pressure, and normal-sized kidneys without dilatation of the urinary tract. Parental consanguinity is another argument.

Renal biopsy shows severe tubular damage on light microscopy. Groups of atrophic tubules with thickened basement membranes alternate with groups of dilated or collapsed tubules. These changes in the tubular basement membranes are highly suggestive of juvenile nephronophthisis (Figure 12.12).[81] Homogeneous or multilayered thickening of tubular basement membranes is prominent, but disintegration of the basement membrane can also occur. There is moderate interstitial fibrosis with few inflammatory cells. The glomeruli are often normal, although secondary sclerosis is observed in advanced disease. Medullary cysts may be present at later stages of the disease (Figure 12.13).

Associated disorders

The Senior–Loken syndrome, in which tapetoretinal degeneration accompanies juvenile nephronophthisis is seen in 15% of cases (Figure 12.14).[82,83] Leber's congenital amaurosis is the early-onset form of the syndrome. The affected children are blind from birth, lack any electroretinogram activity, and develop retinitis

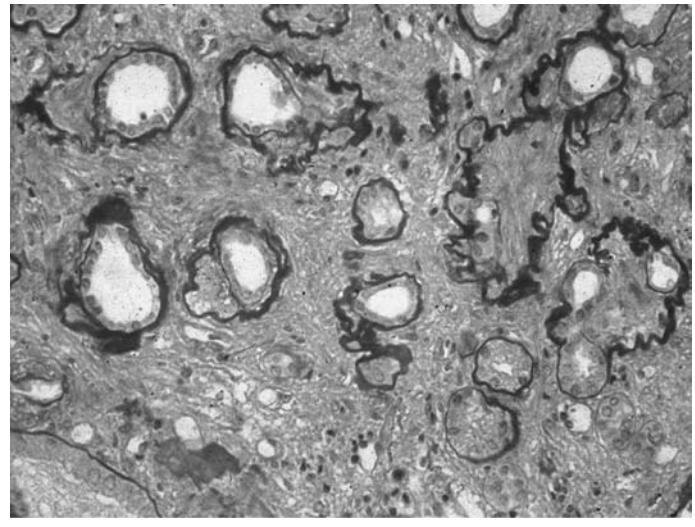

Figure 12.12 A cross-section of the kidney showing shrunken cortex and medulla in nephronophthisis. Cysts of variable size are present in the medulla and the corticomedullary junction.

Figure 12.13 Light microscopy of renal biopsy in nephronophthisis showing irregularly thickened tubular basement membranes and marked interstitial fibrosis.

pigmentosa (Figure 12.15).[84] In the late-onset form, blindness occurs later during childhood. Other eye anomalies have been reported in association with juvenile nephronophthisis and include coloboma, cataract, amblyopia, and nystagmus.

Cerebral involvement, which is usually accompanied by retinal degeneration, can lead to mental retardation and cerebellar ataxia. Cogan syndrome is the triad of nephronophthisis, ocular apraxia, and cerebellar ataxia. In Joubert syndrome, nephronophthisis is accompanied by retinal coloboma or retinitis pigmentosa.[85] Bone anomalies can lead to cone-shaped epiphyses, which are usually associated with other extrarenal manifestations (Saldino–Mainzer syndrome).[86] Hepatic involvement consists of hepatosplenomegaly and portal fibrosis with no or only mild bile duct proliferation.[87–89]

Genetics

In 1993, a gene responsible for juvenile nephronophthisis was localized on chromosome 2q13.[90] Homozygous deletions of about 250 kb in the 2p12 region are detectable in 70% of patients,[91] which facilitated identification of the responsible gene, NPHP1, in 1997.[92,93] The detection of such homozygous mutations permits a fast and accurate diagnosis of the disease without the need for a renal biopsy. Heterozygous deletions are found in 15% of patients with concomitant point mutation of the NPHP1 gene on the second allele. The NPHP1 gene contains 20 exons and encodes a protein named nephrocystin-1, a coil-coiled protein with a role in protein interactions and in cellular adhesion to extracellular matrix. Mutations of NPHP1 have been observed in patients with moderate tapetoretinal degeneration. NPHP1 deletions have been found in patients with Cogan syndrome.[94]

Genetic heterogeneity for patients with or without extra renal symptoms have been demonstrated and since 2001 several new genes have been identified (Figure 12.16). NPHP4 is a 30 exon gene located on chromosome 1p36, which encodes a 1426 amino acid protein called nephrocystin-4.[95] NPHP4 mutations have been identified in families with the Senior–Loken syndrome as well.[96] Nephrocystin-4 interacts with nephrocystin-1 and is probably involved in the same intracellular signaling pathway. The finding of NPHP1 or NPHP4 mutations in some patients with Cogan syndrome or retinal abnormalities indicates an important function of both genes in the central nervous system.

Otto et al recently identified mutations in the IQB1 gene, now referred to as NPHS5, in patients with Senior–Loken syndrome.[97] All patients with mutations in this gene have retinitis pigmentosa. IQB1 encodes an IQ-domain protein, which interacts with RPGR (retinitis pigmentosa GTPase regulator), expressed in photoreceptor cilia.

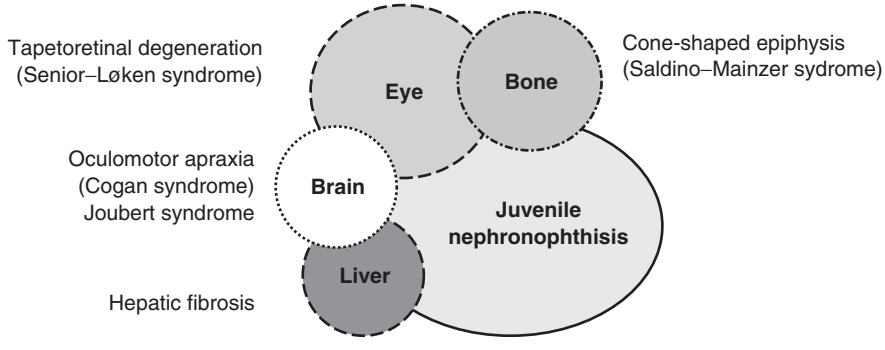

Figure 12.14 Extrarenal symptoms associated with juvenile nephronophthisis.

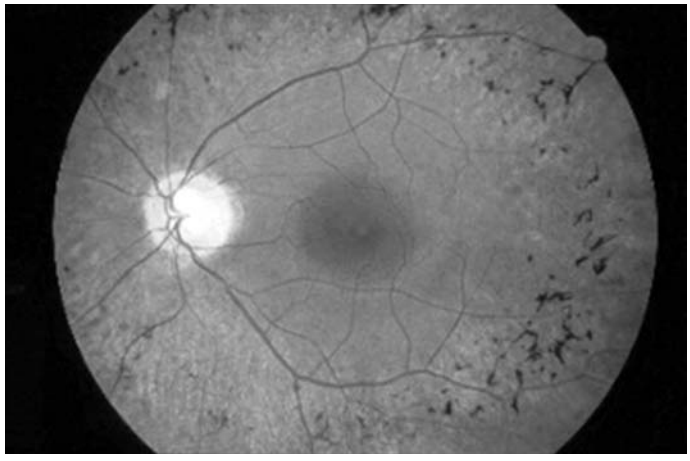

Figure 12.15 Photograph of the retina showing the changes seen in tapetoretinal degeneration.

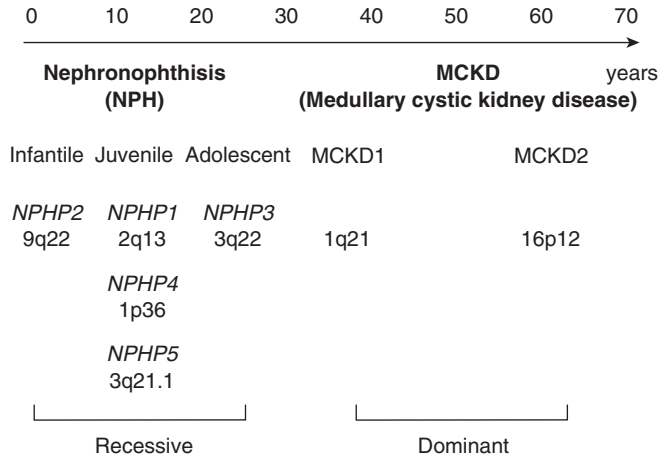

Figure 12.16 Nephronophthisis and medullary cystic disease complex.

Heterogeneity of nephronophthisis

Infantile nephronophthisis

A chronic autosomal recessive tubulointerstitial nephritis with cortical microcysts progressing to ESRF before 2 years of age was initially described by Gagnadoux et al.[98] This disorder is now known as *infantile nephronophthisis*, and is caused by mutations in the NPHP2 gene. This gene, which encodes inversin, is located on chromosome 9q22-31.[99] Inversin interacts with nephrocystin and is located in the cilia. Inversin acts as a molecular switch between different Wnt signaling cascades.[100] The disease differs from nephronophthisis not only by its early onset but also by the histopathologic features. Whereas cystic dilatations of the collecting ducts are seen in these patients, the typical changes in the tubular basement membranes seen in juvenile nephronophthisis are absent.

Adolescent nephronophthisis

A new gene NPHP3, located on chromosome 3q21-22, has been identified recently in a large family of nephronophthisis patients from Venezuela.[101] The NPHP3 mutations are transmitted as an autosomal recessive trait responsible for a clinical variant of *adolescent nephronophthisis*. NPHP3 encodes a protein which interacts with nephrocystin. Interestingly, mutations in the mouse ortholog Nphp3 result in polycystic kidney disease.

Medullary cystic kidney disease

Medullary cystic kidney disease (MCKD) differs from nephronophthisis by the absence of extrarenal symptoms. MCKD is characterized by an autosomal dominant mode of inheritance. Histologic features of MCKD are similar to nephronophthisis. Although the clinical manifestations of MCKD and nephronophthisis are similar, progression to ESRD occurs after the age of 20 years. One gene, MCKD1, has been located on chromosome 1q21.[102] Mutations in the MCKD2 or UMOD gene located on chromosome 16p12 have been detected in families with juvenile hyperuricemic nephropathy and gout.[103,104] The UMOD gene encodes uromodulin or Tamm–Horsfall protein.

Mitochondrial disorders

Mitochondrial disorders (mitochondrial cytopathies) are genetic defects of oxidative phosphorylation which can affect different organs or tissues.[105,106] These disorders have long been regarded as neuromuscular diseases. However, a number of other organs, including the heart, liver, pancreas, hematopoietic system, and kidney, are dependent upon mitochondrial energy supply and can, therefore, be affected during the course of these disorders (Table 12.4).[107] Several clinical entities encompassing mitochondrial disorders have been described according to the clinical presentation (Table 12.5). Renal involvement and symptoms are more common in children than in adults.

Reabsorption of water and solutes in the kidneys is an energy-dependent process. Kidneys, whose weight represents less than 1% of the body mass, consume 10% of total body oxygen.[108] The energy needed for solute and water reabsorption comes from oxidative reactions that produce ATP. Mitochondrial oxidative phosphorylation accounts for 95% of the total ATP production in the kidney. ATP is essential to drive the sodium–potassium-ATPase pumps that generate the electrical gradient across proximal tubular epithelium and keeps the interior of the cell at a low concentration of sodium compared with the outside. These gradients drive the metabolic activity of the proximal tubular cell. All the other absorptive functions for glucose, phosphate, amino acids, etc., are handled through co-transporters.

Table 12.4 Clinical symptoms observed in patients with mitochondrial cytopathies

Affected organ	Symptoms
Central nervous system	Apnea, lethargy, hypotonia, coma in the neonatal period Hypotonia, psychomotor regression, cerebellar ataxia, stroke-like episodes, myoclonus, seizures, dementia, spasticity, headache, hemiparesis in infants and children
Muscle	Myopathy, poor head control, limb weakness, myalgia, exercise intolerance
Liver	Liver enlargement, hepatocellular dysfunction
Heart	Cardiomyopathy, heart block
Kidney	Proximal tubulopathy, nephrotic syndrome, renal failure, tubulointerstitial nephritis
Gut	Vomiting, diarrhea, villous atrophy, colonic pseudo-obstruction, exocrine pancreas dysfunction
Endocrine	Diabetes mellitus, growth hormone deficiency, hypoparathyroidism, hypothyroidism
Bone marrow	Sideroblastic anemia, neutropenia, thrombocytopenia
Ear	Hearing loss
Eye	Progressive external ophthalmoplegia, pigmentary retinal degeneration, ptosis, diplopia, cataract
Skin	Mottled pigmentation, trichothiodystrophy

Table 12.5 Clinicopathologic entities in mitochondrial cytopathies

Kearns–Sayre syndrome	Progressive external ophthalmoplegia, retinal pigmentary degeneration, cerebellar ataxia, heart block
MERRF (myoclonus epilepsy and ragged-red fibers)	Encephalomyopathy with myoclonus, epilepsy, ataxia, myopathy, hearing loss, and dementia
LHON (Leber's hereditary optic neuropathy)	Blindness, cardiac dysrythmia
MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)	Headache, vomiting, lactic acidosis, myopathy with ragged-red fibers, seizures, dementia, deafness
Leigh disease	Subacute necrotizing encephalomyopathy, ataxia, respiratory troubles with weak cry, deafness, blindness
CPEO (chronic progressive external ophthalmoplegia) and mitochondrial myopathy	Ocular myopathy, retinal pigmentary degeneration, central nervous system dysfunction
Alpers' disease	Progressive infantile poliodystrophy, hepatic failure

Therefore, it is not surprising that the most frequent renal defect in mitochondrial diseases is a proximal tubulopathy.

Clinical manifestations

Tubulopathy

The most frequent renal manifestation of mitochondrial disorders is proximal tubulopathy, resulting in a more or less complete and severe form of De Toni–Debré–Fanconi syndrome.[109,110] The De Toni–Debré–Fanconi syndrome includes urinary losses of amino acids, glucose, proteins, phosphate, uric acid, calcium, bicarbonate, potassium, sodium, and water. The proximal tubulopathy is often moderate, and several authors have reported isolated hyperaminoaciduria in the absence of clinical manifestations. Some patients, however, show non-anion gap metabolic acidosis, hypophosphatemia, hypercalciuria, glycosuria, and tubular proteinuria. Some patients may also develop growth retardation, rickets, or dehydration.

Extrarenal symptoms are always present and include myopathy, neurologic symptoms, Pearson syndrome, diabetes mellitus, or cardiac problems. Most patients develop tubular symptoms before the age of 2 years and over 40% of them die during the first year of life. Several reported cases had neonatal onset.[111–113]

Renal biopsy (Figure 12.17) demonstrates non-specific abnormalities of the tubular epithelium, with dilatations and obstructions by tubular casts; de-differentiation, or atrophy of the tubular cells, is also seen. Giant mitochondria are often observed within the tubular cells in light microscopy as well as electron microscopy.

Nephrotic syndrome

Children with mitochondrial disorders may present with steroid-resistant nephrotic syndrome and FSGS (Figure 12.18).[114,115] Several authors have described children with the triad of steroid-resistant nephrotic syndrome, hypoparathyroidism, and sensorineural deafness.[116,117] The patients reported by Barakat et al had an autosomal recessive mode of inheritance and progressed to ESRD during early childhood.[114] They had extrarenal symptoms such as myopathy, ophthalmoplegia, pigmentary retinopathy, and cardiomyopathy. Some patients may even present with congenital nephrotic syndrome.[118]

Coenzyme Q_{10} deficiency was reported in two siblings with severe encephalopathy, nephrotic syndrome, and renal failure. As the in-vitro addition of quinone to cultured fibroblasts stimulated respiration and enzyme activities, the patients were treated with oral ubidecarenone and improved dramatically.[119]

Tubulointerstitial nephropathy

Tubulointerstitial nephropathy has been described in a few patients with mitochondrial disorders.[120–122] The clinical presentation is characterized by polyuria due to impaired urinary concentrating ability, and by progression to ESRD. These patients usually do not show proximal tubular defects. Renal biopsy shows diffuse interstitial fibrosis with tubular atrophy and sclerotic glomeruli within the area of interstitial fibrosis. Extrarenal symptoms consisting of hearing loss, cardiomyopathy, myopathy, growth retardation, mental retardation, and pigmentary retinopathy can also be seen.

Metabolic investigations

Plasma lactate and ketone bodies

Since the respiratory chain transfers a proton (H+) from NADH to oxygen, a disorder of oxidative phosphorylation results in an altered oxidoreduction status in plasma. This feature is a consequence of the functional impairment of the Krebs cycle, due to the excess of NADH and the lack of NAD, with the secondary elevation of blood lactate and increase of ketone bodies and lactate/pyruvate molar ratios in affected individuals. This is particularly true in the postabsorptive periods, when more NAD is required for the adequate metabolism of glycolytic substrates. Similarly, as a consequence of the Krebs cycle impairment, ketone body synthesis increases after meals, instead of decreasing, due to the channeling of acetyl CoA toward ketogenesis. Consequently, the screening for mitochondrial disorders includes the determination of lactate, pyruvate, ketone bodies, and their molar ratios in both fasted and fed individuals.

However, these metabolic abnormalities may not be present in patients with proximal tubulopathy because the impaired proximal tubular functions may increase urinary lactate and lower blood lactate. For this reason, normal plasma lactate does not rule out a mitochondrial disorder with proximal tubulopathy. In these cases, the clue to the diagnosis comes from the association with other related symptoms. Gas chromatography–mass spectrometry can detect high amounts of lactate and Krebs cycle intermediates in the urine.

Enzymologic investigations

Polarographic and spectrophotometric studies allow identification of the biochemical nature of the mitochondrial defect.[123] Polarography measures oxygen consumption by mitochondria in the presence of various oxidative substrates. The only limitation of this technique is that it requires fresh tissue. Spectrophotometric studies assess isolated or combined respiratory chain complexes using specific electron donors and acceptors. Ideally, the affected tissue is the one that should be studied.

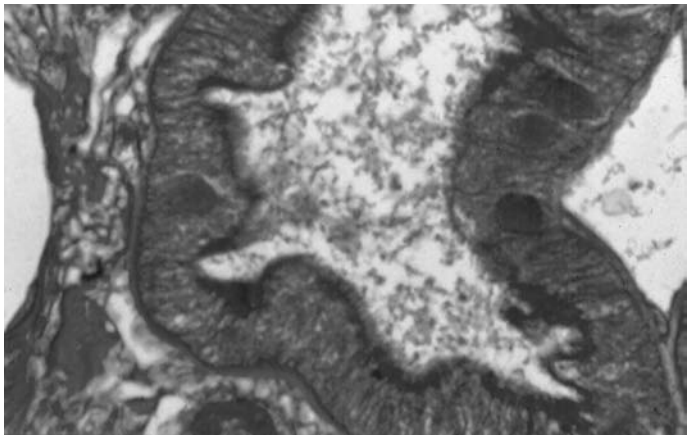

Figure 12.17 Light microscopy of renal biopsy in mitochondrial cytopathy and proximal tubulopathy.

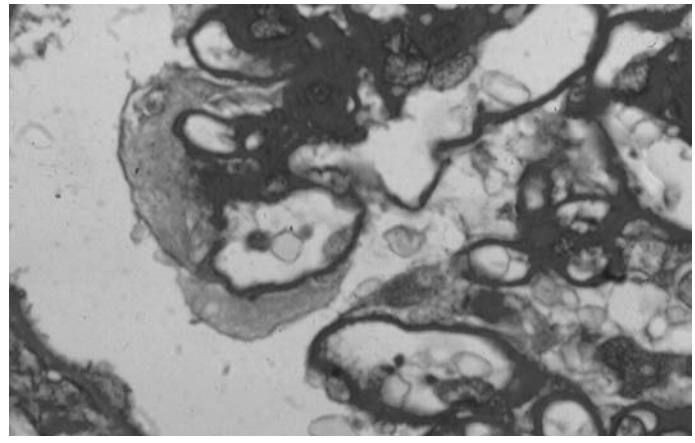

Figure 12.18 Light microscopy of renal biopsy in mitochondrial cytopathy and nephrotic syndrome showing hypertrophic podocytes.

However, when the disease is expressed in organs difficult to access, such as the kidney, accessible peripheral tissues should be extensively tested (including skeletal muscle, cultured skin fibroblasts, and circulating lymphocytes).

Respiratory chain analysis can identify the defective complex(es). No specific enzyme deficiency is associated with renal disease, but complex III or multiple respiratory chain deficiencies are more frequent in patients with renal symptoms.

Genetic basis of mitochondrial disorders

Any mode of inheritance (autosomal recessive, dominant, X-linked, maternal, or sporadic) can be observed in mitochondrial disorders.[124] Mutations in both mitochondrial and nuclear genes have been identified in patients with mitochondrial disorder-associated renal involvement. However, the molecular definition is complicated by the dual genetic control of respiratory chain proteins and by the high number of genes involved in the biogenesis and assembly of the respiratory chain. Therefore, mutations are identified in only a very few cases.

The A3243G change in the tRNALeu gene is one of the most commonly encountered mitochondrial DNA (mtDNA) point mutations (MELAS mutation). This mutation is maternally inherited and is heteroplasmic. It can be associated with a large variety of clinical phenotypes, including nephrotic syndrome. Large mtDNA deletions have been described in several patients with renal disease. There are only a few examples of kidney disease associated with nuclear gene mutations.

Concluding remarks

The exponential growth in our scientific knowledge and techniques of investigation of genetic diseases has made it possible to understand the mechanisms behind the development of many known inherited renal diseases. Diagnostic gene testing, as well as prenatal testing, is available for some of these disorders. The next frontier to be conquered is to develop therapeutic interventions that can prevent and cure such genetic diseases, such as minimal change nephrotic syndrome, and urologic malformations, such as dysplasia and vesicoureteric reflux, can be determined in future, and targeted therapies for their cure can be developed.

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13 Immunoglobulin A nephropathy and Henoch–Schönlein purpura nephritis

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Immunoglobulin A nephropathy (IgAN) is the most frequent type of chronic glomerulonephritis in children,[1] whereas Henoch–Schönlein purpura (HSP) is the most common childhood vasculitic condition, with nephritis being its most common chronic manifestation.[2] Due to shared pathogenic features, IgAN and HSP nephritis (HSPN) are discussed together in this chapter.

Historical perspective

In 1968 Jean Berger reported IgA deposition in the mesangial region of glomeruli from children and young adults experiencing macroscopic hematuria during a viral upper respiratory infection (URI).[3] In this report Berger also described similar IgA deposits in patients with HSP.[3] Some children followed after the diagnosis of HSPN subsequently had one or more episodes of macroscopic hematuria in the absence of rash, joint, or abdominal symptoms.[4] Meadow and Scott reported identical twins with simultaneous adenovirus infections.[5] One of the twins had the clinical phenotype of HSP and the other had isolated macroscopic hematuria, but both had mesangial IgA deposits. HSP has occurred in children who previously had one or more episodes of isolated macroscopic hematuria,[6,7] with an interval of as long as 12 years between the episode and the onset of HSP.[7]

Epidemiology

Few studies have determined population-based incidence for IgAN in children and adolescents; some studies have relied upon inferences from the percentage of cases in renal biopsy series. In Memphis, Tennessee and Seoul, Korea the incidence was about 10%,[1,8] whereas in Japan it was considerably higher, at about 25%.[9,10] In central and eastern Kentucky, from 1985 through 1994, the incidence of IgAN was 5.6 cases per million persons per year (MPPY) for children aged 1–9 years old and 10.2 cases/MPPY for those aged 10–19 years old.[11] In Yonaga City, Japan, from 1983 to 1999, the incidence was 45 cases/MPPY for children under age 15.[12] The increased incidence in Japanese compared with US children might reflect a racial difference in incidence. However, more likely explanations include increased detection through school screening programs, better diagnostic acuity of Japanese primary care physicians, and an aggressive approach of Japanese pediatric nephrologists towards biopsies for children with isolated microscopic hematuria or low levels of proteinuria.

Data from adult biopsy series suggested that IgAN is rare in persons of African descent[13] and very few cases of IgAN have been reported from the continent of Africa.[14] However, in Shelby County (Memphis), Tennessee, for the period 1985 through 1995, the incidence of IgAN was higher for African-American children than Caucasian children (5.7 vs 3.0 cases/MPPY, respectively).[15] We continue to diagnose a significant number of African-American patients with IgAN.[16]

Population-based incidence for HSP from different regions was more than 100 cases/MPPY, or at least 20-fold higher than that of IgAN.[1] However, since only 20–40% of children with HSP develop nephritis, which is often mild, the incidence of persistent HSPN appears similar to or even lower than that of IgAN.

Most pediatric studies of IgAN find a male-to-female predominance of about 2 to 1.[17–20] However, Japanese data

that include school screening programs found no male predominance.[12] Males and females are affected equally with HSP,[1] but for HSPN there appears to be a slight male predominance of about 1.5 to 1.[21–25]

Pathogenesis and genetics

Recent evidence implicates a deficiency in galactose residues in the hinge region of IgA1 as the basic pathophysiologic defect in IgAN and HSPN.[26–28] Human IgA exists in two subclasses: IgA1 and IgA2. IgA1 differs from IgA2 and the other immunoglobulins in that it has a hinge region that contains *O*-linked glycans composed of *N*-acetylgalactosamine (GalNAc) linked to galactose (Figure 13.1). Attachment of the galactose requires β1,3-galactosyltransferase. Galactose-deficient IgA1 can be detected in serum samples from patients with IgAN and HSPN by an increased affinity for binding to various lectins such as the lectins from *Helix aspersa* that are specific for terminal GalNAc.[28,29] Patients with IgAN also have circulating immune complexes that contain galactose-deficient polymeric IgA1 (pIgA1).[30] IgA1-containing immune complexes may deposit in the glomerular mesangium by virtue of decreased clearance from the circulation and/or increased affinity for binding to mesangial structures.[31–33]

Mesangial IgA deposits typically recur in renal allografts with recurrent IgAN, sometimes causing late graft loss.[34,35] IgAN has been diagnosed in a patient with a renal allograft after HSPN progressed to end-stage renal disease (ESRD).[36] When an allograft from a donor with IgAN was transplanted, the IgA deposits resolved over several months.[37]

In 1985 we described a pedigree containing 8 patients with IgAN who descended over 200 years from one of the earliest settlers of Pike County, Kentucky.[38] Many similar pedigrees were subsequently described from eastern Kentucky[39] and northern Italy.[40] A study of the French Society of Nephrology described 40 families in which two or more first-, second-, or third-degree relatives had IgAN, with 5 families having a

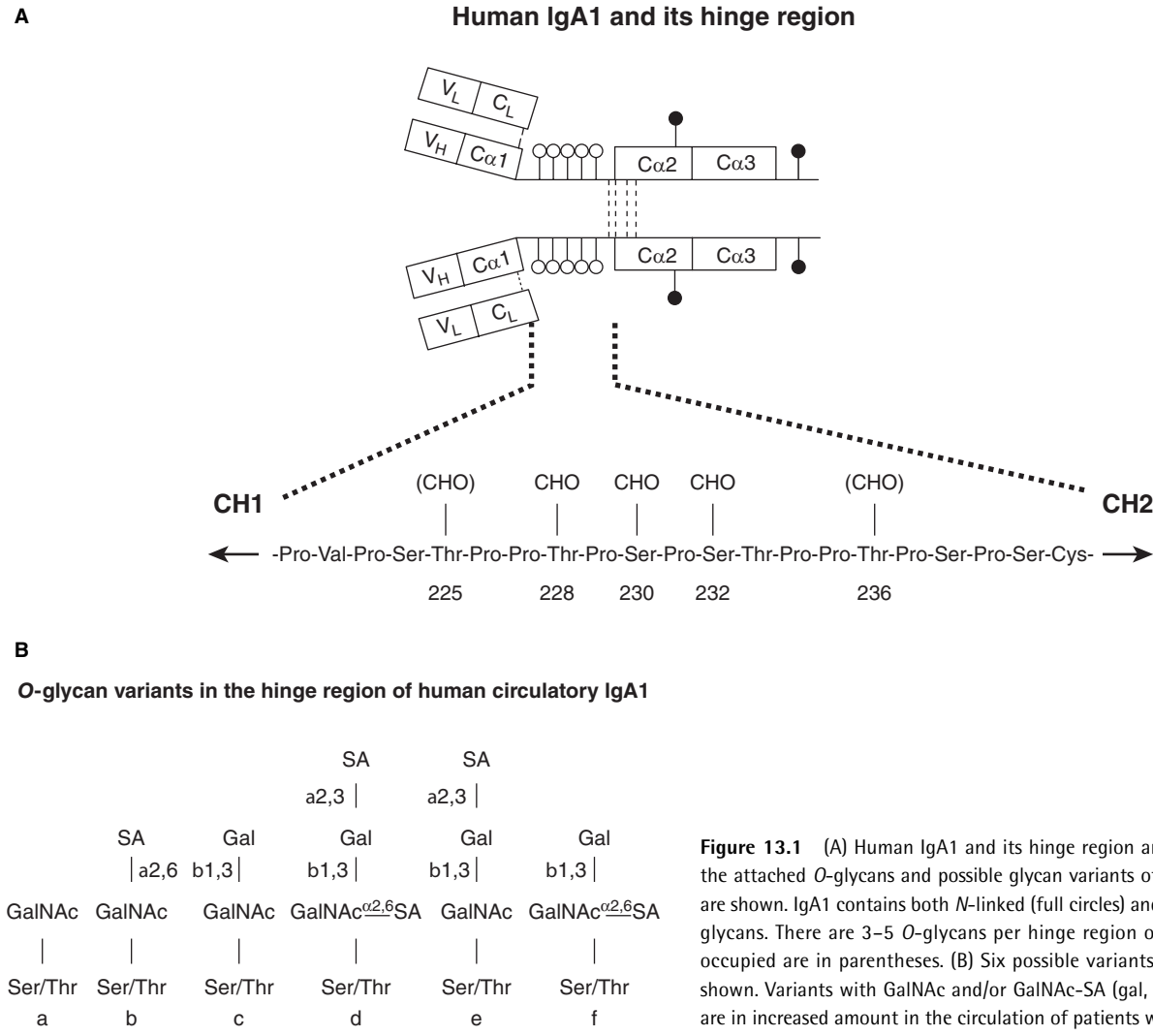

Figure 13.1 (A) Human IgA1 and its hinge region amino acid sequence with the attached *O*-glycans and possible glycan variants of human circulatory IgA1 are shown. IgA1 contains both *N*-linked (full circles) and *O*-linked (empty circles) glycans. There are 3–5 *O*-glycans per hinge region of IgA1. Sites not always occupied are in parentheses. (B) Six possible variants of *O*-linked glycans are shown. Variants with GalNAc and/or GalNAc-SA (gal, galactose SA, sialic acid) are in increased amount in the circulation of patients with IgAN and HSPN.

member with HSP.[41] In addition, 18 other families had one member with IgAN and one or two with HSP. In 1999, Gharavi et al used members of 30 pedigrees from Italy and Kentucky to demonstrate linkage to a locus on chromosome 6 in 60% of the pedigrees.[42] This locus at 6q22-23 was named *IgAN1*. However, no gene or gene product from that locus of pathogenic importance for IgAN has yet been identified. Nevertheless, genetic factors are clearly involved in the predisposition to or clinical expression for IgAN and HSPN.[43]

Pathology

In both IgAN and HSPN, IgA is the dominant or co-dominant immunoglobulin that deposits in the glomerular mesangium.[21,44] Figure 13.2 shows this mesangial pattern as demonstrated by direct immunofluorescence (IF). These deposits can almost always be seen by electron microscopy, typically in the paramesangial region where the basement membrane covers the mesangium. Only the IgA1 subclass is found in the deposits. The immune deposits may also occur in the capillary loops, particularly during the early phase of aggressive HSPN and IgAN.[45,46] Light microscopic features are quite variable: glomeruli may have normal histology, mesangial proliferation without glomerular sclerosis or other chronic changes, focal segmental glomerulosclerosis with or without mesangial proliferation, adhesion of the glomerular tuft to Bowman capsule, and formation of crescents (Figure 13.3). Classification systems such as the one used by the Southwest Pediatric Nephrology Study Group (SPNSG) for IgAN grade biopsies from 1 to 3, with grade 1 denoting normal or minimal glomerular change, grade 2 only mesangial proliferation, and grades 3 or higher for the various chronic focal glomerular lesions.[47–49] The presence of chronic tubular and interstitial injury is not often seen in the initial biopsy for pediatric IgAN and HSPN, but when present indicates potentially chronic and progressive disease.[50]

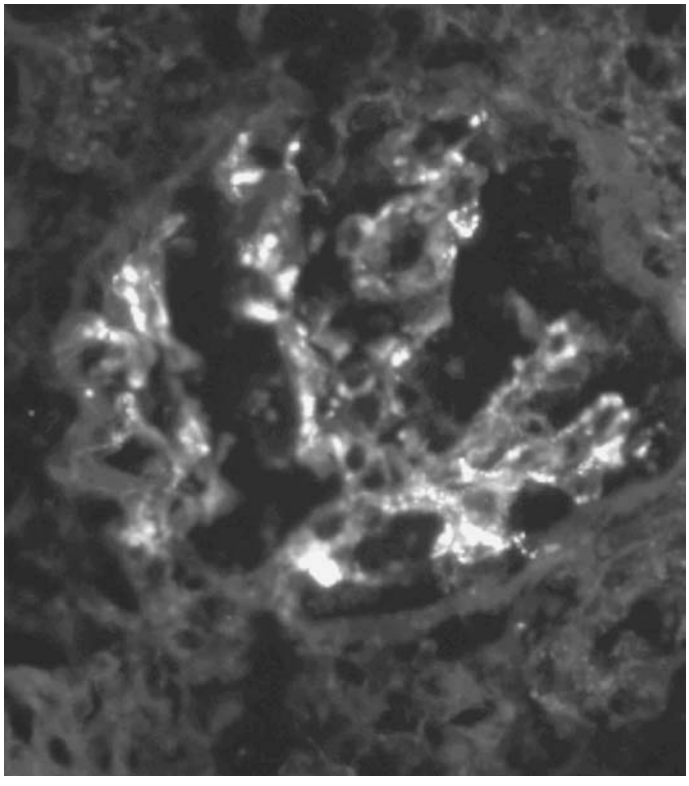

Figure 13.2 Glomerulus showing the typical mesangial staining for IgA by direct immunofluorescence.

Clinical manifestations

In the United States, 75% of children and adolescents with IgAN present with macroscopic hematuria.[18,50,51] Such episodes typically occur during a URI, with the macroscopic hematuria clearing after a period of 2–4 days. Other presentations include microscopic hematuria and proteinuria, isolated microsopic hematuria, and asymptomatic proteinuria. About 10% of children presenting with macroscopic hematuria have transient renal insufficiency,[18] but less than 5% have chronic renal insufficiency (CRI) at diagnosis.[18,50] Prior to the widespread use of normative blood pressure data based upon gender, age, and height percentiles, hypertension at presentation of pediatric IgAN appeared to be rare. The use of such normative data suggests that about 25% of US patients are hypertensive at presentation.[52] However, severe hypertension in children presenting with normal renal function is rare. As a result of school

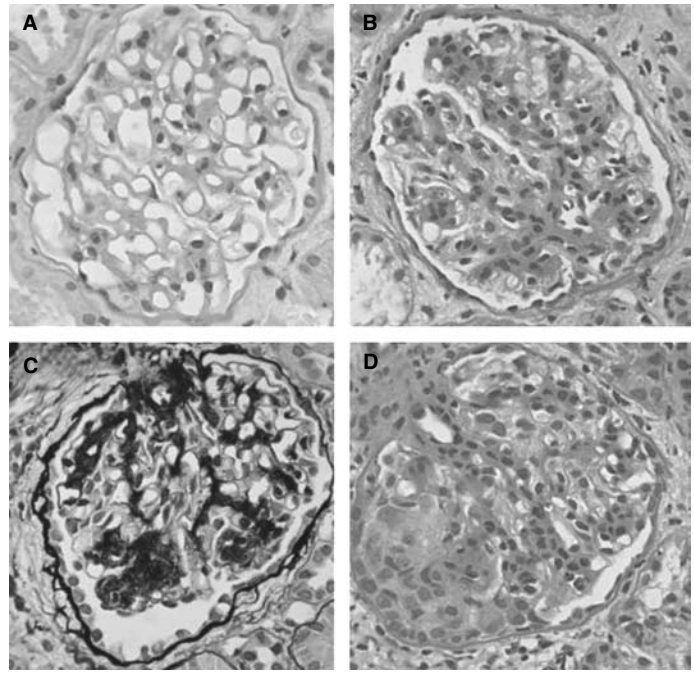

Figure 13.3 (A) Normal glomerulus. (B) Pure diffuse mesangial proliferation. (C) Focal segmental glomerulosclerosis. (D) Epithelial crescent.

screening programs, the majority of the cases in Japan are detected with asymptomatic microscopic hematuria and/or proteinuria.[9,12] Some children detected by screening may subsequently have a typical episode of macroscopic hematuria during a URI.

IgAN and steroid-responsive idiopathic nephrotic syndrome (SRINS) have occurred in the same child, and the clinical manifestations of one may appear several years after the other.[53,54] Treatment with corticosteroids should be directed toward the SRINS and not withheld due to the presence of IgAN.[54]

The peak incidence of HSP is between 4 and 6 years of age, although individuals may present later in childhood or even as adults. When the child initially presents with the typical rash (Figure 13.4) and other manifestations such as abdominal pain or arthritis, the urinalysis is often normal even in those who subsequently develop severe nephritis. HSPN may actually develop after all other manifestations of HSP have resolved.[55] Thus, it is imperative that all patients with HSP should have a urinalysis performed every other week for at least 2 months from onset. Approximately 25% of children with HSPN will have macroscopic hematuria.[1,56] For pediatric patients, those with HSPN are more likely than those with IgAN to develop the nephrotic syndrome: 10–20% for HSPN[56–58] compared with 7% for IgAN.[18,19]

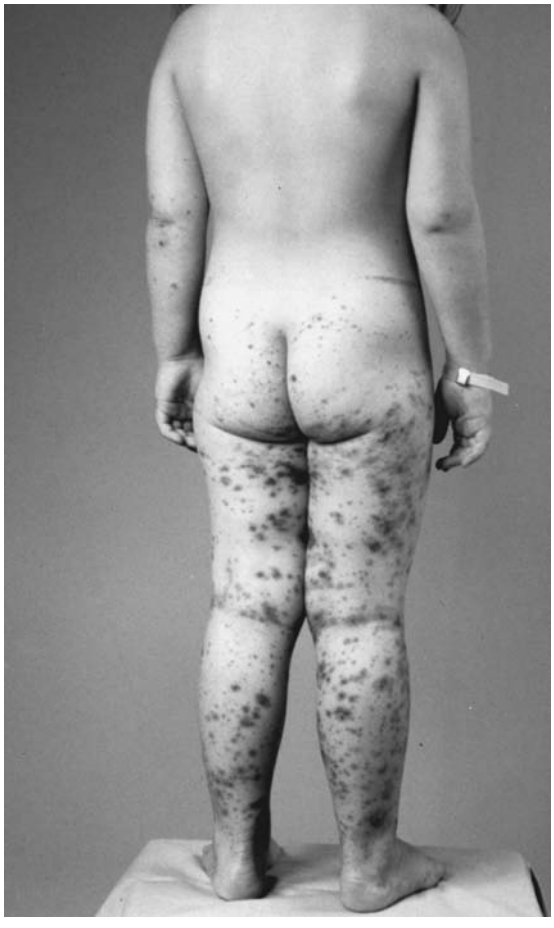

Figure 13.4 Photograph showing the characteristic distribution of rash in a child with HSP.

Evaluation

There is no specific serologic marker for IgAN; diagnosis depends on IF examination of cortical renal tissue. In contrast, the diagnosis of HSPN is based upon the presence of typical clinical features of HSP and clinical evidence of nephritis.[59] In HSPN, renal biopsy is usually reserved for patients with significant nephritis who may require treatment. The renal biopsy findings in HSPN and IgAN are indistinguishable,[21,60] although patients with HSPN are more likely to have significant crescentic involvement.[1,21]

For suspected IgAN, initial laboratory tests should include serum creatinine and albumin, serum C3, fluorescent antinuclear antibody (ANA) to exclude systemic lupus erythematosus (SLE), and urinalysis and quantitation of urinary protein excretion by either a timed urine collection or random protein-to-creatinine ratio. Except in the rare instance of pre-existing deficiencies of an individual complement component or regulatory protein, serum concentrations of C3 and C4 are normal in both IgAN and HSPN.[17,21,61,62] For HSPN, p- and c-ANCA (antineutrophil cytoplasmic antibodies) and platelet counts may be necessary. Although serum IgA level is usually above the mean and often significantly elevated in both IgAN and HSPN,[17, 21] the sensitivity and specificity are too low for its use as a diagnostic test.

The differential diagnosis of IgAN includes C1q nephropathy,[16,63] IgG nephropathy, and SLE.[64] Poststreptococcal acute glomerulonephritis rarely presents with a rash that appears similar to the HSP rash, and this diagnosis should be entertained when the serum C3 level is depressed.[65] Another unusual presentation is HSPN with typical systemic manifestations but without mesangial immune complex deposition.[21]

Outcome

The outcome for pediatric patients with IgAN ranges from complete resolution of all clinical signs of disease to ESRD.[17,18,46,50,52,66–68] At least one-third of pediatric patients with IgAN eventually have a normal urinalysis,[17,18,50,52,66,67] including some with SPNSG grade 3 histology and/or nephrotic range proteinuria at diagnosis.[52] Survival data for pediatric IgAN, although limited, indicate that 20% of patients eventually progress to ESRD, often as adults.[18,67,68] In Japan, 5% of pediatric patients with IgAN reach ESRD by 10 years from diagnosis.[67,68] Our initial data for 48 patients followed in Lexington, Kentucky and 55 patients in Memphis, Tennessee predicted 13% reaching ESRD 10 years from the first sign of disease.[18] Current data for the Memphis cohort of 97 patients showed 15% reaching ESRD at year 10 and 27% reaching ESRD at year 20 from biopsy (Figure 13.5).

Precise outcome for HSPN is difficult to determine due to wide differences in severity of cases reported from various tertiary care hospitals. Data from 'unselected' patients suggest that the risk of ESRD is about 1% for all children with HSP and 3% for those with HSPN.[56,57,69] Clearly, some pediatric patients with HSPN will progress to ESRD; up to 25% have been reported in several biopsy series.[21,23–25,47,70,71] In Germany, 22% of patients with HSPN were predicted to reach ESRD by 10 years from onset.[24]

Prognostic indicators

The optimal primary endpoint for studies of prognostic markers and treatment of glomerular diseases is progression to ESRD or a surrogate marker that closely associates with this endpoint. For pediatric IgAN, clinical markers at diagnosis that associate with progression to CRI and/or ESRD are: (1) degree of proteinuria and (2) severe histologic features such as the presence of crescents and/or segmental sclerosis.[18,46,50] Hypertension was significantly related to progression in only one report.[50] Two reports that both included the same patients from Memphis suggested that African-Americans had a significantly worse outcome than Caucasians.[18,50] However, for Memphis patients diagnosed since 1990 there was no difference in outcome based upon race.[16] Our most recent kidney survival data for the entire Memphis IgAN cohort show no difference in progression to ESRD based upon gender.

For HSPN, severe histology and nephrotic syndrome are markers of poor prognosis.[21,71] Logistic regression analysis in a German cohort found that renal insufficiency at presentation and nephrotic syndrome were significant independent predictors of outcome.[24] Although many clinicians feel that younger children are less likely to have severe or progressive HSPN, age at presentation does not significantly associate with outcome.[23,24,47]

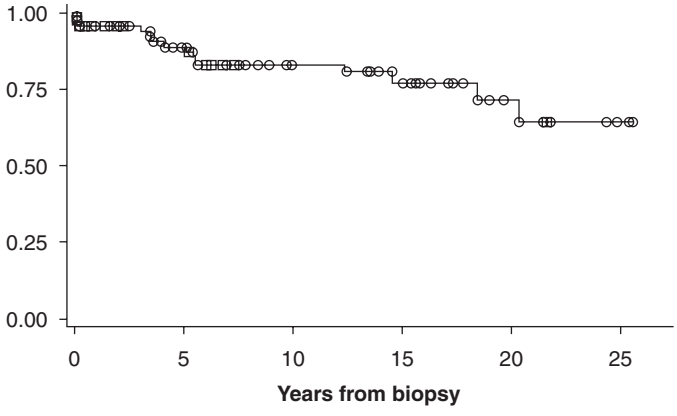

Figure 13.5 A Kaplan–Meier curve for percent kidney survival from time of diagnostic biopsy for 97 pediatric patients with IgA nephropathy. Circles on the curve represent time of last follow-up for the patients who did not progress to end-stage renal disease.

Several immunogenetic markers for prognosis have been examined in pediatric studies of IgAN and HSPN.[1,52,72–79] Since serum angiotensin-converting enzyme (ACE) levels are partly determined by ACE genotype, many studies of ACE genotype have been done in both children and adults with IgAN and pediatric HSPN. Although several studies, including one from our group, suggest an association between the DD genotype and outcome, unequivocal immunogenetic markers for prognosis do not yet exist.[52,72–79]

Treatment

There is no clear evidence-based guidelines for the treatment of pediatric IgAN and HSPN.[54] This is due to such factors as (1) the small number of patients at single centers; (2) the difficulty, time, and expense in organizing randomized controlled trials; and (3) the progression from normal function to chronic kidney disease (CKD)/ESRD may take several decades. In addition, distinct treatment strategies may be applied to acute and chronic phases of disease.

Figure 13.6 depicts the approach to the treatment of IgAN and HSPN used in our center. Rapidly progressive or severe crescentic IgAN and HSPN are usually treated with high-dose intravenous methylprednisolone pulses followed by oral corticosteroids and sometimes other immunosuppressive agents such as cyclophosphamide.[54,80–84] All published data on this

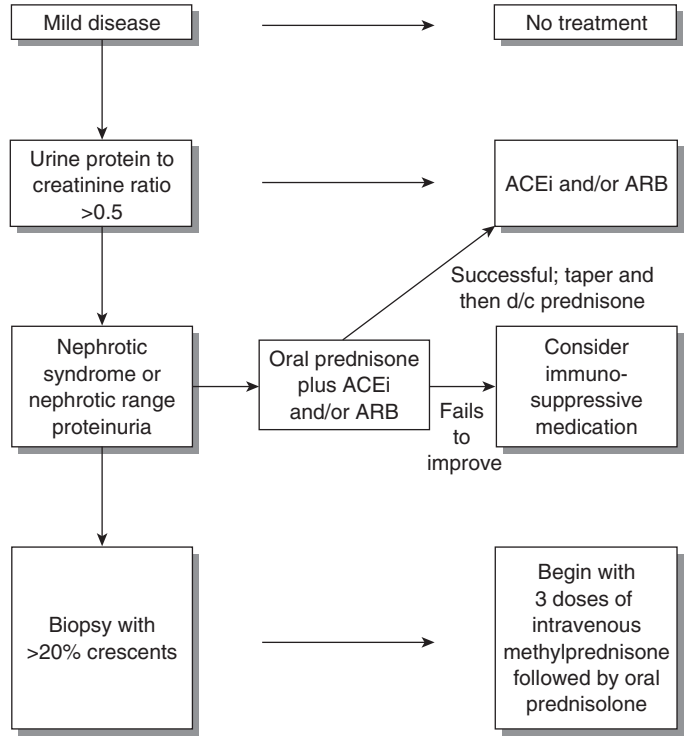

Figure 13.6 Approach to the treatment of IgA nephropathy and HSP nephritis.

approach are from uncontrolled case series. This treatment may be effective in some instances, but a poor outcome cannot be avoided if the glomerular lesions are too far advanced before therapy is begun.[54]

Treatment with an ACE inhibitor (ACEi) or angiotensin receptor blocker is recommended as initial therapy for adults with IgAN.[85,86] Our group and others now use this approach for both hypertensive and normotensive pediatric patients.[54,87] In an ongoing randomized controlled trial of mycophenolate mofetil (MMF) for pediatric and adult patients with IgAN, many subjects have such significant reduction in proteinuria in response to 3 months of ACE inhibitor and fish oil treatment that they are no longer eligible for randomization to MMF or placebo (Reference 88 and RJ Hogg, pers comm). Results previously attributed to corticosteroids can probably be achieved by ACE inhibitors alone.

Although there are no randomized controlled trials (RCTs) that support the approach, corticosteroid therapy is indicated for pediatric patients with IgAN or HSPN who have the nephrotic syndrome.[54,89] A recently completed randomized controlled trial for adult and pediatric patients with IgAN compared alternate-day prednisone, fish oil capsules, and placebo.[90] There was no significant advantage with respect to time to ESRD for any arm of the trial.[91]

Case report

A previously well 5-year-old Caucasian male presented with the typical features of HSP: purpuric rash distributed on the lower limbs, swollen ankles, abdominal pain, and microscopic hematuria. Two weeks later he developed macroscopic hematuria. He had transient hypertension, with a maximum blood pressure of 120/85 mmHg that resolved without treatment. Pertinent laboratory tests included the following: hemoglobin, 11.3 g/dl; platelet count, 519×10^9/ml; serum creatinine, 0.5 mg/dl; serum albumin, 2.8 g/dl; serum cholesterol, 242 mg/dl; C3, 92 mg/dl (normal), and a negative ANA test. The urinalysis had a specific gravity of 1.015 with 2+ protein and a sediment that showed too numerous to count (TNTC) red blood cells (RBCs), 5–10 white blood cells (WBCs)/hpf and several granular casts/lpf. Random urine protein to creatinine (Up/c) ratio increased from 0.62 to 4.1 over the next 7 days. Renal biopsy showed diffuse mesangial proliferative glomerulonephritis with focal sclerosis in 9% and cellular crescents in 12% of the glomeruli. IF showed mesangial deposition of IgA (3+), IgG (2+), C3 (3+), and properdin (2+). Alternate-day prednisone was begun at a dose of 40 mg/m^2 every other day and continued in a tapering dose for 18 months. At this time ACE inhibitor was not used for treatment of non-hypertensive glomerular disease. One month after treatment was stopped, the urine had TNTC RBC/hpf, but the Up/c ratio was normal (0.13).

The child was not seen again until age 10 when he had an episode of macroscopic hematuria associated with exercise. At this time, he had no rash, joint, or abdominal symptoms. His serum creatinine was 0.5 mg/dl and he had a Up/c ratio of 2.8. Alternate-day prednisone was again begun at 40 mg/m^2 per dose and fish oil supplement (MaxEPA) was added. After 4 months he was lost to follow-up until he returned at age 14 years old after another episode of macroscopic hematuria during a flu-like illness. His serum creatinine was 0.9 mg/dl and albumin was 3.1 g/dl. Urinalysis showed specific gravity of 1.020 with 2+ protein. Microscopic examination of unspun urine showed TNTC RBCs/hpf, 20% of which were dysmorphic. The Up/c ratio was 4.1. A second renal biopsy showed diffuse mesangial proliferation, with 20% obsolescent glomeruli, but minimal focal sclerosis and no crescents. There was minimal intersitial fibrosis. The IF pattern was similar to that of the first biopsy except for the presence of IgM in 1+ intensity. He was normotensive, with no HSP rash. With no therapeutic intervention, 2 weeks after the biopsy the Up/c ratio fell to 1.07 and 10 mg/day of the ACE inhibitor fosinopril was begun.

One year later he had yet another episode of macroscopic hematuria with a viral illness. Over the next 2 months his serum creatinine increased from 0.7 to 2.2 mg/dl and albumin fell to 2.9 g/dl and the Up/c ratio was up to 5.9. A third renal biopsy was performed, which showed diffuse mesangial proliferation, with 10% of the glomeruli having cellular crescents. Several glomeruli showed segmental sclerosis and fibrous adhesions to Bowman capsule. Alternate-day prednisone at 40 mg/m^2 per dose and MMF (initial dose of 600 mg/m^2/day, advanced to 900 mg/m^2/day) were started. The prednisone was discontinued after 10 months and MMF after 14 months when the serum creatinine was 0.7 mg/dl, albumin was 3.2 g/dl, and the Up/c was 2.5. Three years later, at age 17, he developed macroscopic hematuria again and the nephrotic syndrome shortly after undergoing a tonsillectomy. Serum creatinine was 1.7 mg/dl, albumin was 2.0 g/dl, and Up/c was 4.6 and he had severe edema with ascites. He slowly improved after treatment with alternate-day prednisone, MMF, fosinopril, and losartan. At the last follow-up, he continued to have microscopic hematuria, with a serum creatinine of 1.1 mg/dl, serum albumin of 3.4 g/dl, and a Up/c ratio of 0.75.

Concluding remarks

As illustrated in the above case report, some patients that originally have HSPN will enter a chronic phase in which the clinical phenotype is that of IgAN. Patients with HSPN and IgAN, with persistent proteinuria and/or flares characterized by macroscopic hematuria during viral illness, appear to be at risk for eventual progression to ESRD. In such cases, decisions about treatment are difficult and sometimes not supported by evidence from RCTs. Future advances will depend upon delineation of the earliest pathogenetic mechanisms in IgAN and HSPN, with specific therapy targeted toward such mechanisms.

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14 Tubulointerstitial nephritis

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The tubulointerstitial structures comprise nearly 80% of the renal parenchyma, and consist of renal tubules and the interstitium. These structures provide support for the nephrons and the renal vasculature. Tubulointerstitial nephritis (TIN) is a heterogeneous disorder, and as a group, tubulointerstitial disorders constitute the most common form of renal pathology.[1] A lower reported incidence of primary TIN may reflect a failure to recognize the disorder on routine renal biopsy.[2] Progression of renal disease, and deterioration of glomerular and tubular functions, correlates well with progressive tubulointerstitial damage.[3–5]

Definition and classification

TIN is a disorder associated with an inflammatory infiltrate, edema, or fibrosis affecting either the renal tubules, or the interstitium, but both are frequently involved.[6] From a clinical perspective, TIN may be acute or chronic in onset:

- *acute tubulointerstitial nephritis (ATIN)* is characterized by an acute inflammatory cell-mediated response that is associated with a rapid decline in renal functions
- *chronic tubulointerstitial nephritis (CTIN)*, also referred to as chronic tubulointerstitial nephropathy, or fibrosis, is characterized by a protracted onset and causes a slow decline in renal function.[7]

ATIN and CTIN may not represent distinctly separate disorders but a continuum in the spectrum of initial acute inflammatory cell-mediated response that transforms into interstitial fibrosis in chronic cases. This transition to fibrosis can occur quickly, and increased intracellular matrix may become evident at 1 week after onset of the disorder.[5] TIN is defined as primary in origin when the inflammation is limited to the tubules and interstitium, where glomeruli and vessels are either not involved, or show minor involvement. Secondary tubulointerstitial nephritis is associated with a primary glomerular or vascular disease.[7]

Epidemiology

The precise incidence of TIN is unclear. It accounts for 8–27% of the reported cases of acute renal failure (ARF) in adults[8–11] and up to 7% in children.[12] Among all asymptomatic army recruits in Finland who underwent renal biopsy, the incidence of ATIN was documented as 0.7 per 100 000.[13] The incidence, however, was higher (1.2%) in individuals with an abnormal urinalysis (hematuria and/or proteinuria).[13] TIN is estimated to account for 22–33% of cases with chronic kidney disease (CKD) in adults.[14,15] CTIN is commonly seen in association with obstructive uropathy[16,17] and vesicoureteral reflux (VUR),[18,19] both of which are significant causes of CKD and end-stage renal disease (ESRD) in children.[20]

ACUTE TUBULOINTERSTITIAL NEPHRITIS

Pathology

Renal biopsy findings in ATIN demonstrate a mononuclear cell infiltrate within the interstitium, most prominently observed in the cortical interstitium (Figure 14.1A). Presence of infiltrating lymphocytes between tubular epithelial cells (tubulitis) is common in severe cases (Figure 14.1B). The interstitial mononuclear infiltrate consists mostly of T lymphocytes, whereas B cells and plasma cells constitute a minor fraction. Eosinophils may be present, especially in drug-induced ATIN. Interstitial granulomas with giant cells may be seen with some drugs (methicillin, thiazides), and sarcoidosis (Figure 14.2). Variable degrees of tubular necrosis and regeneration are usually present. Lymphocytes may be observed in the tubular lumen. The glomeruli are generally normal, but nephrotic syndrome with minimal change has been reported in some cases of TIN caused by non-steroidal anti-inflammatory drugs (NSAIDS).[21] In ATIN due to infections, neutrophils may dominate as the cell type. Interstitial edema may be observed.

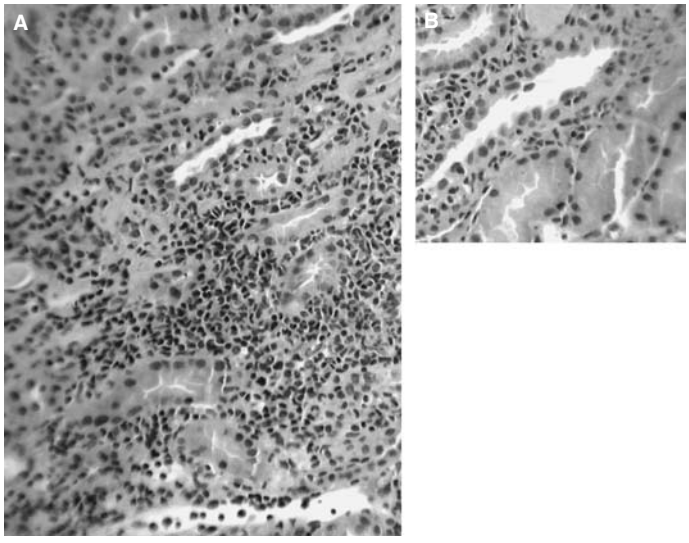

Figure 14.1 (A) Light microscopy showing acute interstitial inflammatory infiltrate consisting of mononuclear cells in a patient with acute interstitial nephritis. The patient presented with acute renal failure and proteinuria. (B) Inflammatory cell infiltration into the tubules resulting in 'tubulitis'. (Courtesy of Ronald M Przygodzki MD, Children's National Medical Center, Washington, DC.)

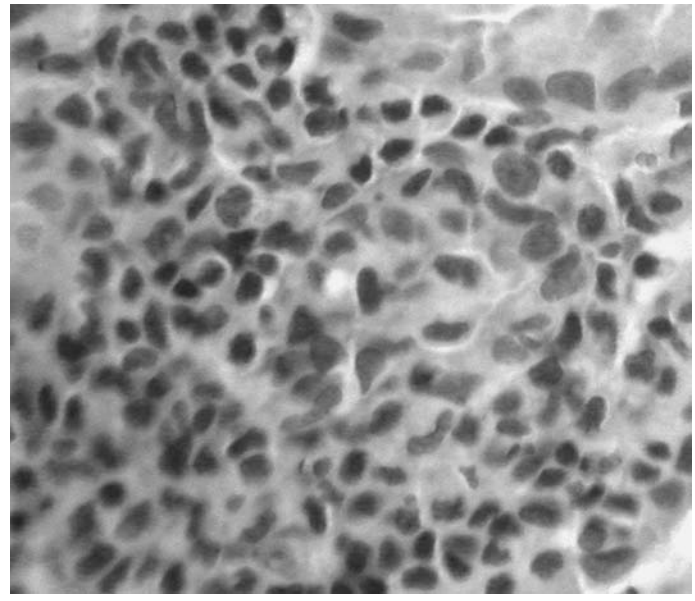

Figure 14.2 Interstitial granuloma in a patient with sarcoidosis. (Courtesy of Ronald M Przygodzki MD, Children's National Medical Center, Washington, DC.)

Based on immunofluorescence findings, ATIN can be classified into three subtypes:

- no antibodies or immune deposits (pauci-immune),
- immune complex deposits present along the basement membrane (Figure 14.3)
- linear immunofluorescence staining for immunoglobulin (IgG) and complement along the tubular basement membrane (TBM), also known as antitubular basement disease (Figure 14.4).[22,23]

Etiology

ATIN may occur in four distinct clinical settings (Table 14.1): exposure to drugs, infections, immunologic disorders, and idiopathic.

Drug-induced ATIN

ATIN associated with exposure to drugs is the most common cause of ATIN in adults.[24,25] Drugs[26] and infections[27–29] are the two leading causes of ATIN in children. The list of drugs reported to cause ATIN is ever expanding (Table 14.2). Of these, penicillins, NSAIDs, rifampin, and sulfonamide derivatives account for the majority of reported cases.[30] Drug-induced ATIN is a rare idiosyncratic reaction and occurs in only a small subset of patients exposed to any specific medication. It is not dose-dependent, and typically occurs with repeated exposure to the drug. Structurally similar drugs may induce cross-reactivity, as evidenced by recurrent ATIN after cephalosporin administration in individuals with previous penicillin-induced ATIN.[30]

Infection-associated ATIN

Infection-associated ATIN may complicate the clinical course of many bacterial, viral, fungal, and parasitic infections (see Table 14.1). It may occur as a result of direct renal infection (pyelonephritis), or as an immune-mediated reaction to a systemic infection. Polyoma BK virus-induced interstitial nephritis has been reported in renal transplant patients.[30] Reactivation of the latent virus in immunosuppressed patients in the renal epithelium is believed to induce interstitial nephritis. The presence of typical basophilic or amphophilic intranuclear inclusions on renal biopsy is diagnostic. Distinguishing polyoma viral infection from graft rejection is critical in the management of these patients.

Immunologically mediated ATIN

Antibodies, immune complexes, or T cells may mediate ATIN by immune mechanisms.[7] Primary tubulointerstitial nephritis resulting from anti-TBM antibody[31,32] and immune complex deposition is rare.[33] Linear deposits of IgG and complement along the TBM, with relative sparing of glomeruli and vessels, characterize primary anti-TBM nephritis.[7] Systemic lupus erythematosus (SLE) is the most important cause of ATIN seen in association with glomerulonephritis in children.[19] Secondary ATIN may also be seen in association with membranous glomerulonephritis, shunt nephritis, and IgA nephropathy.[7] Patients with tubulointerstitial involvement have worse renal function than those with isolated glomerular involvement.[34] Allograft rejection, tubulointerstitial nephritis with uveitis (TINU), and sarcoidosis present with predominant tubulointerstitial damage secondary to T-cell mechanisms.[7]

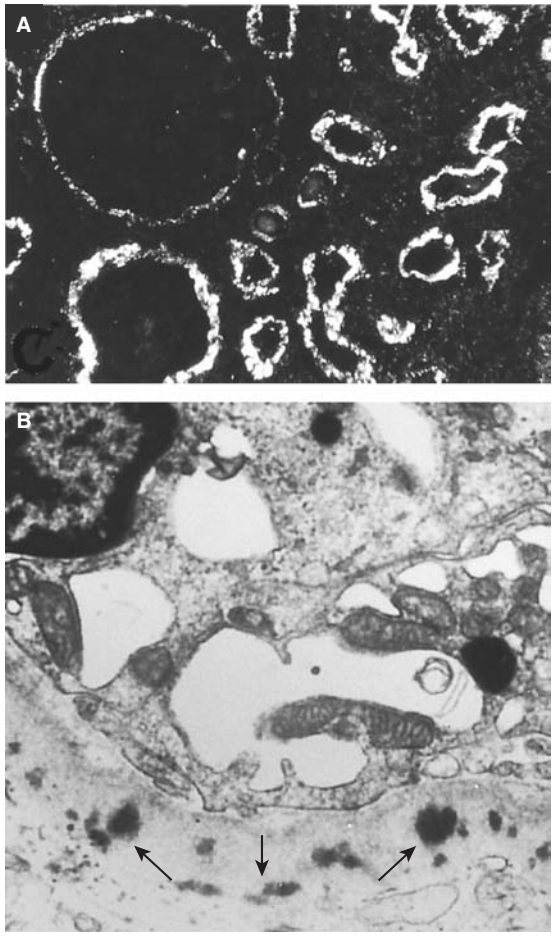

Figure 14.3 (A) Immunofluorescence staining showing granular immune deposits of immunoglobulin G in a patient with tubulointerstitial nephritis. (B) Electron photomicrograph showing numerous electron-dense deposits (arrows) in the basement membrane of the proximal tubule. (Reproduced with permission from the Amer J Kid Dis, 34(1), Markowitz GS, Seigle RL, D'Agati VD. Three-year-old boy with partial Fanconi syndrome. 184–8, 1999 with permission from National Kidney foundation.)

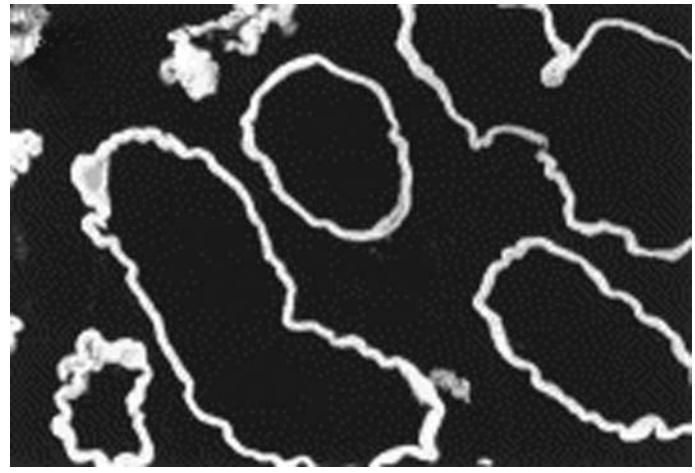

Figure 14.4 Immunofluorescence microscopy showing linear immunoglobulin G deposits in a patient with acute interstitial nephritis. (Tokumoto M. Fukuda K, Shinozaki M, et al. Acute interstitial nephritis with immune complex deposition and MHC class II antigen presentation along the tubular basement membrane. Nephrol Dial Transplant, 1999, 14(9), 2210, by permission of Oxford University press.)

Pathogenesis

The immune reaction producing tubulointerstitial damage, like any other immune-mediated reactions, has an antigen recognition phase, immune regulatory phase, and the effector phase (Figure 14.5).

Antigens

The antigens causing TIN may be derived from the interstitial cells, or may be 'planted' into the interstitial microenvironment from the circulation. The nephritogenic antigens derived from the renal cells and the TBM include 3M-1 antigen,[35] Heymann nephritis protein (gp330, megalin),[36] and Tamm–Horsfall protein.[37–39] 3M-1 (TIN antigin) is the antigen of anti-TBN disease and has been characterized and mapped to chromosone 6 in humans.[35] Immunohistochemical studies have indicated that TIN antigen is defective in kidney tissues of patients with juvenile nephronophthisis.[39] Allotypic differences in the expression of the gene may occasionally result in anti-TBM disease in renal transplants of these patients.[40,41] Tamm–Horsfall protein may be an inciting antigen, especially following lower tract obstruction.[42]

Molecular mimicry of infectious agents,[43,44] drugs acting as haptens,[45] or toxic damage to the interstitium exposing cryptic nephritogenic neoantigens,[46] are other mechanisms whereby tubulointerstitial antigens may become targets. Studies have also shown that induction of TIN could be a consequence of viral proteins as in EBV-[47] and HIV[48]-related renal disease. Experimental evidence suggests that native renal cells can process and present the antigen to T cells,[49,50] up-regulate cell surface proteins, including ICAM[51] and VCAM,[52] and enhance production of cytokines and chemokines.[53] Induced class II MHC (major histocompatibility complex) expression by renal tubular cells in response to inflammation or proinflammatory cytokines[49,54] may promote autoimmune injury by facilitating expression of self-antigens.

Immune response

Genetic factors play a role not only in antigen expression[55] but also in immune response to a particular antigen[56] (immune response genes). Successful recognition of antigens leads to activation of nephritogenic T cells, which sequentially activates the nephritogenic immune response. Regulation of autoimmune B- and T-cell response may occur either during the maturational phase or by a fully differentiated effector mechanism. Interstitial nephritis is relatively uncommon, as nephritogenic T- and B-cell activation is self-limited by down-regulatory events.[56,57] These regulatory events include complementary interactions in immune system,[57] or regulation of target antigen presentation.[58] The immune response genes carried by specific

Table 14.1 Etiologic classification of acute tubulointerstitial nephritis

Drug exposure (see also Table 14.2)
- Immunologic mechanisms – antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics
- Toxic mechanisms – aminoglycosides
- Unknown mechanisms

Infections

Reactive (sterile nephritis, infective agent not in renal parenchyma):
- Bacteria – *Yersinia pseudotuberculosis*, *Mycoplasma*, *Streptococcus pneumoniae*, β-hemolytic streptococcus, *Salmonella*
- Viruses – rubella, Epstein–Barr virus (EBV), HIV, hepatitis
- Parasites – *Toxoplasma gondii*, *Leishmania donovani*

Infectious (infection of renal parenchyma):
- Bacteria – Pyelonephritis, *Leptospira*, *Mycobacteria*, *Treponema pallidum*
- Viruses – Cytomegalovirus, Adenovirus, Polyoma BK virus
- Fungi – *Candida*, *Histoplasma capsulatum*, *Aspergillus* sp.
- Rickettsiae – *Rickettsia ricketsii*, *Rickettsia conorii*, *Rickettsia prowazekii*
- Parasites – *Plasmodium* spp., *Schistosoma* spp.

Immunologic

Anti-TBM antibodies:
- Primary anti-TBM nephritis
- Secondary anti-TBM nephritis:
  - Membranous GN
  - Anti-GBM disease
  - Miscellaneous GN

Immune complex deposition:
- Primary immune complex nephritis
- Secondary immune complex nephritis:
  - SLE
  - Sjögren syndrome
  - Membranous GN
  - MPGN
  - Miscellaneous GN

T-cell mechanisms:
- Primary T-cell nephritis:
  - Allograft rejection
  - TINU
  - Sarcoidosis
- Secondary T-cell nephritis:
  - Associated with nephropathies
  - Tubulointerstitial nephritis

Idiopathic

TBM, tubular basement membrane; GN, glomerulonephritis; GBM, glomerular basement membrane; SLE, systemic lupus erythematosus; MPGN, membranous glomerulonephritis; TINU, tubulointerstitial nephritis with uveitis.

individuals are important in determining the host immune response. Suppressor T cells are an important component of the immunoregulatory process. Models of autoimmune interstitial nephritis provide evidence for peripheral inactivation of autoreactive clones regulating suppressor T cells.[59] Breakdown of the tolerance to self-parenchymal antigens is needed for spontaneous TIN, and the details of these mechanisms need to be elucidated.

Effector mechanisms

Cell-mediated response

The predominant effector mechanism in acute interstitial nephritis is cell-mediated immunity. The majority of the infiltrating cells (>50%) in TIN are T lymphocytes; the CD4/CD8 ratio is at least 1, and the infiltrating T cells and tubular epithelial cell express class II MHC. Studies in animal models of TIN have revealed that nephritogenic helper T cells producing interstitial nephritis are usually CD4 and class II restricted,[60] whereas the effector cells are usually CD8 and class I restricted.[61,62] They induce toxic cellular damage by releasing inflammatory cytokines or by direct cell-mediated cytotoxicity by releasing proteases.[61]

Antibody-mediated response

Antibody-mediated damage is less common and may occur as anti-TBM nephritis or immune complex-mediated TIN. Human anti-TBM nephritis has been reported in patients who received drugs such as methicillin, postrenal transplantation, or without underlying abnormality.[31,45,63,64] Immune complex and complement deposition is seen in patients with SLE.[65] Tamm–Horsfall protein[37,38] and Heymann antigen of brush border[36] have been implicated in local immune complex formation in the interstitium. Tamm–Horsfall protein is localized in the interstitium in the setting of urinary tract obstruction or reflux nephropathy, suggesting that it may be a target antigen in previously damaged kidneys.[66]

Amplification of tubular damage and interstitial fibrosis

Infiltration of T cells or antibody-mediated damage triggers the processes that augment and amplify tubulointerstitial injury and inflammation. These include chemoattraction of inflammatory cells such as eosinophils and macrophages, release of soluble factors, and activation of the complement cascade. The soluble factors include chemokines, complement, luminal proteins, cytokines (profibrotic and proinflammatory), and proteinases.[67] Interstitial fibrosis is the final common pathway, especially for diseases associated with glomerular proteinuria or presence of inflammatory cells in the tubulointerstitium.[68,69] Transforming growth factor beta (TGF-β) is the most important profibrotic cytokine.[70] Specific inhibition of TGF-β in ureteral obstruction[71] reduces renal fibrosis. Myofibroblasts play an important role in elaboration of interstitial fibrosis and may evolve from transdifferentiation of tubular epithelial cells (TEC) into fibroblasts (epithelial to mesenchymal transformation), resident interstitial cells, macrophages, or endothelial cells.[67] Immune-mediated mechanisms or various cytokines may trigger this transformation as well as result in tubular cell damage. Thus, tubular atrophy and interstitial fibrosis coexist. Recently, there has been an increase in the knowledge of the role of tubulointerstitium in progressive renal disease. A better

Table 14.2 Drugs that are known to be associated with acute tubulointerstitial nephritis

Antimicrobial agents
Acyclovir
AMPICILLIN[ab]
Amoxicillin
Aztreonam
Carbenicillin
Cefaclor
Cefamandole
Cefazolin
Cefixitin
Cefotaxime
Cefotetan
Cephalexin
Cephaloridine
Cephalothin
Cephapirin
Cephradine
CIPROFLOXACIN
Cloxacillin
Colistin
Co-trimoxazole[b]
Erythromycin
Ethambutol
Foscarnet
Gentamicin
Indinavir
Interferon
Isoniazid
Lincomycin
METHICILLIN[b]
Mezlocillin
Minocycline
Nafcillin
Nitrofurantoin[b]
Norfloxacin
Oxacillin[b]
PENICILLIN G[b]
Piperacillin
Piromidic acid
Polymyxin acid[b]
Quinine
RIFAMPICIN[b]
Spiramycine[b]
SULFONAMIDES
Teicoplanin
Tetracycline
Vancomycin

NSAIDS
Alclofenac
Azapropazone
ASPIRIN
Benoxaprofen
Diclofenac
Diflunisal[b]
Fenclofenac
FENOPROFEN
Flurbiprofen
IBUPROFEN
INDOMETHACIN
Ketoprofen
Mefenamic acid
Meloxicam
Mesalazine (5-ASA)
NAPROXEN
Niflumic acid
Phenazone
PHENYLBUTAZONE
PIROXICAM
Pirprofen
Sulfasalazine
Sulindac
Suprofen
TOLEMETIN
ZOMEPIRAC

Analgesics
Aminopyrine
Antipyrine
Antrafenine
Clometacin[b]
Floctafenin[b]
Glafenin[b]
Metamizol
Noramidopyrine

Anticonvulsants
Carbamazepine
Diazepam
Phenobarbital
PHENYTOIN[b]
Valproate sodium

Diuretics
Chlorthalidone
Ethacrynic acid
FUROSEMIDE[b]
Hydrochlorothiazide[b]
Indapamide
Tienilic acid[b]
Triamterene[b]

Miscellaneous
ALLOPURINOL[b]
Alpha-methyldopa
Azathioprine
Bethanidine[b]
Bismuth salts
Captopril[b]
Carbimazole[b]
Chlorpropamide[b]
Cyclosporine
CIMETIDINE
Clofibrate
Clozapine
Cyamethazine[b]
D-penicillamine
Fenofibrate[b]
Gold salts
Griseofulvin
Interferon
Interleukin-2
OMEPRAZOLE
PHENINDIONE[b]
Phenothiazine
Phenylpropanolamine
Probenecid
Propranolol
Propylthiouracil
Ranitidine
Streptokinase
Sulphinpyrazone
Warfarin

[a]Drugs most commonly involved are shown in capital letters.
[b]Drugs that can induce granulomatous AIN.
Table adapted from and reproduced with permission from Rossert J. Drug-induced acute interstitial nephritis. Kidney Int 60: 804, 2001.
NSAID, Non-seteroid anti-inflammatory drugs.

understanding of the factors involved and these interactions would help in elucidating therapy targets for future use.

Clinical manifestations (Table 14.3)

Manifestations of ATIN can range from asymptomatic proteinuria to ARF. Many patients have associated constitutional symptoms, such as fever (especially during infection-associated ATIN), fatigue, anorexia, weight loss, nausea, and vomiting (Table 14.3).[26–29] About 30–40% of the patients with ATIN have non-oliguric renal failure.[11] ATIN should be suspected in any patient who presents with ARF of uncertain etiology. With drug-induced ATIN, the patient may exhibit other features of the allergic process such as rash, fever, or eosinophilia. A recent study revealed that the classic triad of fever, arthralgia, and rash occurred in only 6 of the 60 (10%) of such patients.[24] Others have noted that in ATIN resulting from penicillin-like drugs, rash was present in less than 50%, fever in 75%, and eosinophilia in 80%, and the entire triad was present in 33% of the patients.[22,72] Such signs of an allergic process, however, are relatively uncommon in ATIN due to NSAIDs.[73]

The urinary abnormalities in ATIN consist of microscopic or macroscopic hematuria, sterile pyuria, and white blood cell casts. Mild proteinuria, usually less than 1 g/day, is frequently observed. Nephrotic range proteinuria with acute disease has occasionally been reported with nephropathies induced by NSAIDs, lithium, ampicillin, and rifampicin.[74] Eosinophiluria, which is defined as the presence of eosinophils greater than 1% of total urinary leukocytes (by Hansel's) stain, may be seen. However, eosinophiluria can be seen in other forms of renal injury and inflammation and is not, by itself, diagnostic of ATIN.[75] Renal ultrasound reveals normal or enlarged kidneys, depending upon the degree of interstitial edema. A gallium scan may show uptake in the kidneys.

Renal tubular epithelial cell damage and abnormalities in tubular functions are common; sometimes these abnormalities may be limited to specific tubular segments.[25] Fanconi syndrome and tubular acidosis are seen rarely in ATIN but are commonly present in CTIN. Urinary β_2-microglobulin excretion is elevated[76,77] and could reflect renal inflammatory activity. In view of the non-specific nature of the clinical and laboratory features of ATIN, a kidney biopsy is often indicated to confirm the diagnosis.

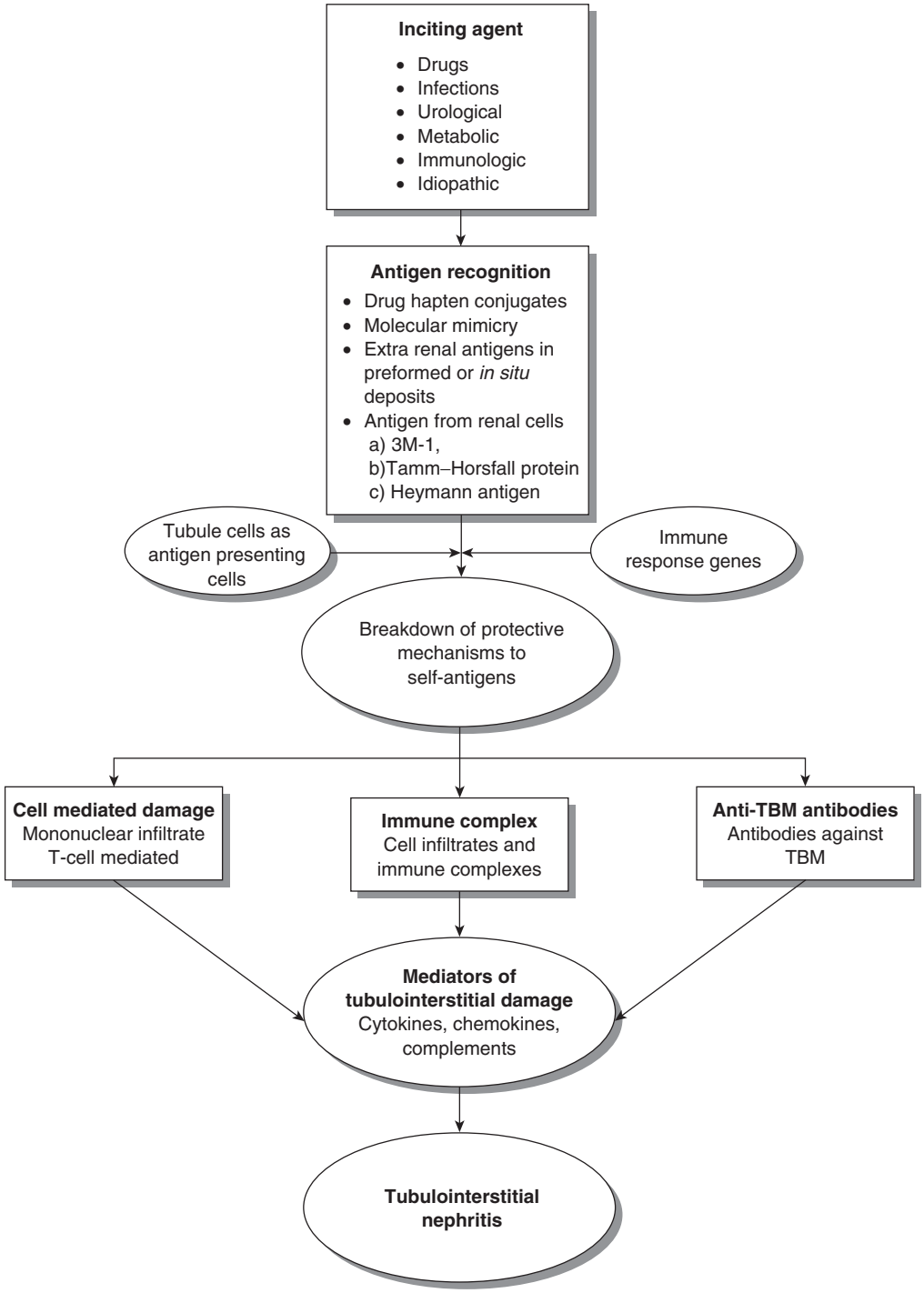

Figure 14.5 Pathogenesis of tubulointerstitial nephritis.

Treatment

The therapy of ATIN should begin by eliminating the possible inciting factors, such as drugs or infections. In choosing therapeutic options, potentially cross-reacting drugs (e.g penicillin by cephalosporin) should be avoided. Many patients with mild ATIN may begin recovery of their renal disease after discontinuation of the inciting drug, and no further treatment may be necessary. Supportive care involving maintenance of fluid balance, monitoring of blood chemistry, and dialysis may be necessary for patients with renal dysfunction. The role of corticosteroids in the treatment of ATIN remains unclear,[9,24,30] despite numerous uncontrolled studies and case reports indicating a beneficial impact of such a therapy.[24] Corticosteroids are generally used as a daily therapy, consisting of oral prednisone (2 mg/kg/day) for 4 weeks, followed by gradual

Table 14.3 Common clinical manifestations of tubulointerstitial nephritis

Symptoms
Anorexia
Vomiting
Abdominal pain
Nausea
Weight loss
Growth failure (CTIN especially)
Eye pain (TINU)
Polyuria
Rash (usually with allergic drug reactions)
Fever

Laboratory features
Urinalysis:
- RBCs, leukocytes, casts
- Urine protein excretion is usually <1 g/day
- FENa is usually > 1

Blood chemistry:
- Increased creatinine
- Predominant segmental tubular defects:
  Proximal tubular defects – proximal RTA, Fanconi syndrome
  Distal tubular defects – hyperkalemia, sodium wasting, distal RTA
  Medullary defects – sodium wasting, polyuria
- Anemia – normochromic normocytic
- Eosinophilia
- Increased erythrocyte sedimentation rate

Radiology:
- Ultrasonography
  Enlarged hyperechoic kidneys (ATIN)
  Small contracted kidneys (CTIN)
- Renal osteodystrophy changes in skeletal radiographs (CTIN)

Renal biopsy:
See text for detail. Diagnostic gold standard

ATIN, acute tubulointerstitial nephritis; CTIN, chronic tubulointerstitial nephritis; TINU, tubulointerstitial nephritis with uveitis; RBCs, red blood cells; RTA, renal tubular acidosis; FENa, fractional excretion of sodium.

tapering.[19,22,30] Methylprednisolone intravenous pulse therapy (5–10 mg/kg/dose) for 1–3 days, followed by oral prednisone, has been used in severe cases of ATIN, especially those with severe acute renal failure.[19,30] There is no available evidence to suggest that cyclosporine or cyclophosphamide is of benefit in patients resistant to steroids.[30]

Prognosis

The prognosis for recovery of renal function after ATIN in children is reported to be excellent.[26,28,29] Poor prognosis in ATIN may be associated with the presence of tubular atrophy.[24,30] However, data on the relationship of interstitial fibrosis[19,30,78–80] and degree of cellular involvement and tubulitis[19,30,81] with the outcome of ATIN is unclear. Poor recovery of renal function has also been reported in patients with protracted oliguria lasting over 3 weeks, and in the presence of a pre-existing renal disease in the patient.[24,81] There is no obvious correlation between peak serum creatinine or clinical severity of the disease at presentation with long-term outcome of ATIN.[19,24]

CHRONIC TUBULOINTERSTITIAL NEPHRITIS

Etiology

CTIN results from numerous infectious, metabolic, structural, toxic, or hereditary factors. CTIN is commonly seen in children in association with obstructive uropathy and VUR. Interstitial damage and progressive fibrosis in these disorders may result from renal immune responses that amplify tubulointerstitial injury, induced by high urinary tract pressures in the setting of infection.[19] Some drugs, such as calcineurin inhibitors (cyclosporine and tacrolimus), are particularly likely to cause CTIN, whereas others can cause both ATIN and CTIN. CTIN due to chronic cyclosporine toxicity is characterized by tubular atrophy, interstitial fibrosis, and vascular hyalinosis and sclerosis.[82] With the exception of cisplatin, none of the drugs that cause acute renal failure commonly results in chronic renal failure.[6] Conditions that may be associated with CTIN are listed in Table 14.4. The hyperosmolar, acidic, and hypoxic environment of the renal medulla favors precipitation of many metabolites (e.g. calcium, uric acid, and oxalate), resulting in tubulointerstitial injury and CTIN.[1]

Pathology

Unlike ATIN, CTIN is a slowly progressive disorder characterized by renal tubular atrophy and interstitial fibrosis. Interstitial inflammatory cells' infiltration may be minimal or even absent. The deposited extracellular matrix consists of a combination of collagen I, III, and V from interstitial fibroblasts, and type IV derived from endothelial and tubular cells.[7] Tubular atrophy with thickened and wrinkled tubular basement membrane is generally present. In contrast to ATIN, glomeruli in CTIN often show ischemic changes with shrinkage of the glomerular tuft, thickening of Bowman capsule, and collagen in Bowman's space (Figure 14.6).[7] Periglomerular fibrosis may be present variably. The end result of CTIN can be small kidneys, with prominent scarring and pelvicalyceal dilatation.

Clinical manifestations

The clinical, laboratory, and radiologic manifestations of CTIN are similar to those observed in ATIN.[19] However,

Table 14.4 Etiologic classification of chronic tubulointerstitial nephritis

Drug-related
- Analgesic nephropathy
- Cyclosporine
- Cisplatin
- Lithium
- Phenacetin
- Propylthiouracil
- Nitrosoureas

Urologic
- Obstruction – Posterior urethral valves:
  - Prune belly syndrome
  - Ureteropelvic junction obstruction
  - Calculi
  - Congenital
- Vesicoureteral reflux

Metabolic
- Oxalate nephropathy
- Urate nephropathy
- Hypokalemic nephropathy
- Hypercalcemic nephropathy
- Cystine nephropathy

Heavy metals
- Lead
- Mercury
- Cadmium

Hereditary
- Alport's syndrome
- Nephronophthisis–medullary cystic disease complex
- Sickle cell disease
- Laurence–Moon–Bardt–Biedl syndrome

Immunologic
All of the immunologic causes listed in Table 14.1

Miscellaneous
- Radiation nephritis
- Balkan nephropathy
- Hypoxic disorders
- Anorexia nervosa
- Hemorrhagic fever

individuals with CTIN often have no evidence of disease until late in the course of renal insufficiency, or may have asymptomatic proteinuria. Non-specific symptoms like weight loss, fatigue, anorexia, and vomiting may be present, and polyuria and polydipsia may be prominent features of the illness. Growth retardation may be a prominent manifestation of CTIN in children.[19] Polyuria resulting from inability to concentrate urine due to chronic tubular dysfunction is a common manifestation, and may lead to nocturnal enuresis and urinary frequency. Renal

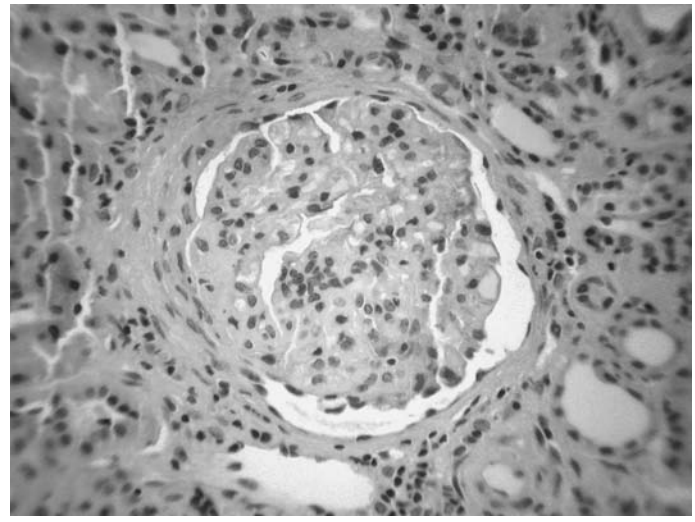

Figure 14.6 Glomerulus in a patient with chronic tubulointerstitial nephritis showing periglomerular fibrosis and ischemic glomeruli with collapsed capillary lumens.

ultrasound usually reveals small and hyperechogenic kidneys. In association with chronic renal insufficiency, skeletal radiographs may reveal changes of renal osteodystrophy. Generally, CTIN tends to progress more slowly than other forms of renal disease.[11]

Treatment

There is currently no known effective therapy for CTIN. As in ATIN, when an offending agent is identified it should be stopped immediately and supportive care initiated. However, the damage may be irreversible and the disease self-perpetuating.[19] Management of hypertension and prevention of further renal damage in the form of infection or from nephrotoxic agents are the focus of treatment. The beneficial effect of angiotensin-converting enzyme (ACE) inhibitors in CTIN-induced proteinuria is yet to be proven.[19]

TUBULOINTERSTITIAL NEPHRITIS UVEITIS

Dobrin et al described the association of tubulointerstitial nephritis with uveitis and granulomas in the bone marrow.[83] This uncommon condition is now recognized as a separate clinicopathologic entity and is known as tubulointerstitial nephritis uveitis syndrome (TINU).

TINU tends to affect young women, but the disorder has been reported in both sexes, as well as in older patients.[84] Renal lesions are characterized by acute interstitial nephritis with predominant T-cell infiltration into the interstitium. Ocular disease is commonly bilateral and is characterized by anterior uveitis. Ocular manifestations can occur before, simultaneous

with, or subsequent to the onset of renal disease. Manifestations of uveitis include ocular pain and visual impairment, and can be the presenting manifestation of the disorder. Fever and other non-specific symptoms such as weakness may also be present.

Laboratory findings are notable for markedly elevated erythrocyte sedimentation rate (ESR), normocytic/normochromic anemia, elevated creatinine, and elevated immunoglobulins. Patients with TINU syndrome have been reported to have serologic evidence of autoantibodies, including antinuclear antibody (ANA), rheumatoid factor, and cytoplasmic antineutrophil cytoplasmic antibodies (cANCA). TINU has also been reported in association with herpes zoster, Epstein–Barr virus (EBV) infection, toxoplasmosis, and insect bites, as well as systemic diseases such as hyper/hypothyroidism, rheumatoid arthritis, and lymphadenopathy. In children and adolescents with this syndrome, TIN spontaneously resolves and its long-term prognosis is good, but uveitis often relapses. Systemic steroids may be required for uveitis, but not for TIN.[84,85]

Concluding remarks

TIN is an important cause of acute renal failure and should be considered in patients with no obvious cause for renal failure. History of infection, drug ingestion, skin rashes, or other constitutional symptoms may be present. Patients may present with renal failure, hypertension, and/or proteinuria. The clinical features are non-specific and strong clinical suspicion is needed to make a diagnosis, which, depending on the clinical course of the patient, may need to be confirmed by renal biopsy. The role of steroid therapy in ATIN is controversial. Elimination of causative agent such as medication and instigation of supportive care are recommended. The prognosis for ATIN is usually good; very few patients progress to CTIN. On the other hand, CTIN indicates chronic progressive renal damage that involves interstitial fibrosis, and glomerular and tubular damage. Recent research has focused on various factors involved in the pathogenesis of TIN and, with better understanding of the immunologic process involved, may help in determining the best targets for treatment.

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15 Hemolytic uremic syndrome

John D Mahan

Hemolytic uremic syndrome (HUS) is characterized by the triad of non-immune microangiopathic hemolytic anemia, thrombocytopenia and renal injury related to the development of platelet thrombi and intravascular coagulation in small vessels, particularly in the renal microcirculation.[1–3] HUS was first described by Gasser et al in 1955[1] and the systemic character of HUS has been well defined by subsequent studies. Kaplan et al identified several distinct entities that can present as HUS, and emphasized that HUS was a 'syndrome' with a common pathologic outcome.[4] HUS is now considered as a part of a broader group of disorders characterized by capillary thrombosis in various organs, known as thrombotic microangiopathy (TMA). HUS is more common in infants and small children, but may occur in older children and adults. Among primary renal disease, HUS remains one of the most common causes of acute renal failure in children.[5,6]

Table 15.1 Causes of hemolytic uremic syndrome

Infectious:
- Shiga toxin (diarrhea +): *Escherichia coli*, *Shigella*
- *Streptococcus pneumoniae* toxin
- HIV

Idiopathic
Familial:
- Factor H deficiency
- Non-factor H deficiency forms

Pregnancy
Vasculitides (including Kawasaki disease)
Malignant hypertension
Transplant rejection
Neoplasia
Medications (cyclosporine, mithramycin, clopidogrel)
Radiation

Clinical classification

Thrombotic microangiopathy encompasses the twin conditions of HUS and thrombotic thrombocytopenic purpura (TTP). Both disorders are characterized by capillary thrombosis and associated organ dysfunction. Although TTP has also been reported in children, it is more common in adults.[7] In contrast, HUS is more common in children but has also been described in adults.

HUS is commonly seen in children with diarrhea and specific bacterial colitis. This is known as diarrhea-positive (D+) HUS. However, some cases of HUS occur in conjunction with a variety of clinical conditions, or therapeutic drug exposure where diarrhea is absent. HUS in such patients is designated as diarrhea-negative (D–) or atypical. Familial forms of HUS are rare and occur almost exclusively in young children; they are most often associated with an inherited defect in von Willebrand factor (vWF) processing.[8,9] Table 15.1 details the classification and types of HUS. Endothelial cell dysfunction is a critical factor in the pathogenesis of platelet aggregation, capillary thrombi formation, vascular injury, and organ dysfunction in all forms of TMA, including HUS.[7,10]

Differentiating hemolytic uremic syndrome from thrombotic thrombocytopenic purpura

The severity of HUS is quite variable, and the degree of renal impairment can range from mild involvement to profound disease with irreversible renal failure. The outcome of children with HUS is also quite variable and is influenced by the underlying etiology.[3,11] The majority of children with HUS display a gastrointestinal prodrome, and neurologic involvement and seizures are uncommon in most cases. Atypical and adult forms of HUS with neurologic manifestations have been reported in children as well. These cases can be difficult to differentiate from thrombotic thrombocytopenic purpura.[12]

In general, neurologic involvement is a clinical hallmark of TTP and distinguishes it from HUS. Recurrence of the disease activity, often triggered by infections, is also more common in TTP, as compared to HUS. Despite the similar clinical presentation, better characterization of the abnormalities in von Willibrand factor in TTP has further allowed a clear distinction between TTP and HUS.[9]

Epidemiology

Approximately 90% of children with HUS manifest D+ HUS that typically presents several days after the onset of a gastrointestinal prodrome that may or may not include bloody diarrhea.[2] D+HUS is mainly a disease of young children, although older children and adults may be affected. There is a slightly increased prevalence in females, especially in adolescents.[3] D+HUS is more common in the spring and summer months, and localized epidemics have been reported from every continent. Based on recent reports, the incidence of D+ HUS remains approximately 0.71/100 000 in the UK,[3] 0.67/100 000 in California,[13] and 0.64/100 000 in Australia.[14] The annual incidence in children < 5 years of age in each country was twice as high.

Shiga toxin

Shiga toxin (Stx)-producing *Escherichia coli* were first linked to acute colitis in humans by Riley et al in 1983[15] and to epidemic HUS in children by Karmali et al in 1985.[16] The most common *E. coli* serotype identified in hemorrhagic colitis and HUS in the United States is O157:H7. By now, over 200 different types of Stx-producing enterohemorrhagic *E. coli* (STEC) have been isolated.[12] STEC toxins are physically similar to the Stx produced by *Shigella dysenteriae* type 1 and this family of toxins are potent inhibitors of protein synthesis in endothelial and epithelial cells.[17,18]

The largest reservoir for STEC is in cattle, in whom it may cause bloody diarrhea but may also exist as a commensal organism.[19] Other potential vectors of STEC include domestic animals (sheep), wild animals (deer, seagulls), humans, water, other unpasteurized beverages, and other food sources. In humans, STEC are associated with both bloody and non-bloody diarrhea as well as systemic HUS. Only about 5–8% of children suffering from hemorrhagic colitis caused by a STEC develop signs of HUS.[20] Virulence factors, such as enterocyte attachment factors, affect the ability of these organisms to produce human disease.[21–23] The subset of STEC that causes enterocolitis and HUS is referred to as enterohemorrhagic *E. coli* (EHEC). The severity of the colitis is correlated with the severity of the TMA and HUS.[24]

Recent studies determined that almost 1% of stool samples in the United States submitted for routine culture are STEC positive and that almost 50% of these are non-*E. coli* O157:H7.[12,25] Stool samples from individuals with bloody diarrhea are more frequently STEC positive.[12,19] STEC can also cause other types of infections, like urinary tract infection.[26] D+HUS has also been caused by isolated cases and epidemics of *Shigella*. Non-O157:H7 *E. coli* have been increasingly defined as sources of Stx in outbreaks of enterocolitis and/or HUS in developed countries.[2,14]

Pathogenesis

D+ hemolytic uremic syndrome

The pathogenesis of D+HUS and the role played by STEC has been clarified in the last two decades. Three distinct forms of Stx, types 1, 2 and 2c, have been identified.[2] These toxins closely resemble the toxin from *Shigella dysenteriae*. Some strains of STEC can produce both types of Stx. This family of toxins were first identified as verotoxins, because they were identified based on toxicity for vero cells (monkey kidney cells) in culture. Shiga toxin is composed of a biologically active subunit A and a number (usually 5) of B subunits, by which the toxin binds to specific glycoprotein receptors on susceptible cells.[20,27]

The typical course of D+HUS is initiated by ingestion of STEC that cause colitis. Stx and lipopolysaccharides are absorbed from the colonic lumen into the systemic circulation (Figure 15.1).[20] Endotoxemia has not been convincingly demonstrated in HUS.[28] Stx binds to glycoprotein galabiosyl ceramide and globotriosyl ceramide (Gb3) receptors on the surface of gastrointestinal epithelial and endothelial cells, as well as renal epithelial and microvascular endothelial cells.[29] The active fragment of Stx (subunit A) is internalized into the cells and interferes with ribosomal protein synthesis and initiates apoptotic pathways, leading to cell death (Figure 15.2).[17,30] Affected endothelial cells also increase the release of von Willebrand multimers into the circulation, which causes platelets to adhere to these multimers and form microvascular clots.[9] Some studies suggest that antibiotic therapy in STEC-mediated gastroenteritis is associated with a higher incidence of subsequent HUS,[31] presumably due to release of Stx into the circulation. However, other studies have failed to demonstrate such a clinical outcome.[32,33]

Stx can also reach the circulation and cause HUS from sites other than gastrointestinal (GI) tract STEC infections.[26] A number of virulence factors associated with specific STEC organisms and types of Stx affect disease severity.[2,21–23]

Stx binding to glomerular and renal tubular cells can be quite variable due to variable cellular Gb3 expression. However, there is no clear evidence to suggest that Stx binding or Gb3 expression is greater in the glomeruli or renal tissue of younger subjects than older individuals.[34] Receptor-mediated internalization of the toxin leads to inhibition of protein synthesis and cellular injury.[27] Other cells exposed to Stx, such as monocytes and neutrophils, are induced to release proinflammatory mediators such as interleukin-1 and TNF and adhere to endothelial cells; these processes may augment the vascular and cellular injury involved in HUS.[35–37] As endothelial surfaces are injured, platelet and coagulation factor deposition results in thrombi formation and, ultimately, the TMA that characterizes HUS.[38]

Non-*E. coli* infection

Some strains of *S. pneumoniae* are capable of producing a neuraminidase that exposes a cryptic T antigen on red blood cells (RBCs), platelets, and endothelial cells.[39] Naturally occurring anti-T antigen antibodies can then react with the exposed T antigens to damage the cells and cause vascular injury and TMA.[40,41] Affected children typically have respiratory infections, and the course of HUS can be variable.

Familial hemolytic uremic syndrome

Children with familial HUS may have a common exposure to an infective agent, such as STEC or *S. pneumoniae*, or an inherited deficiency or dysfunction of factor H.[42,43]

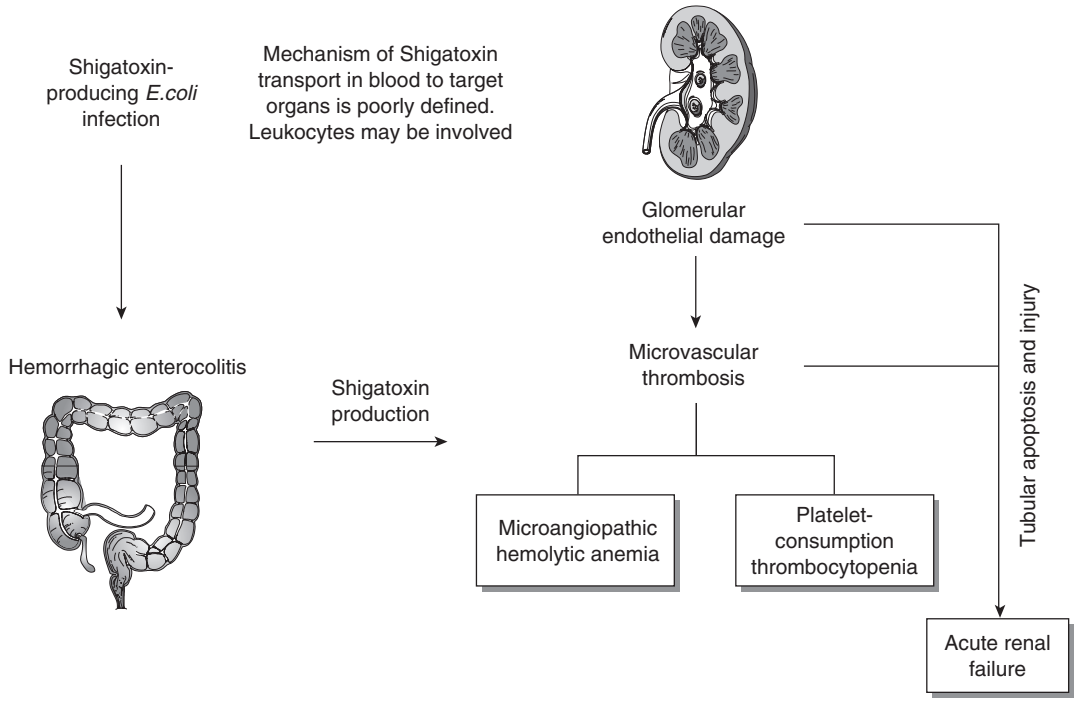

Figure 15.1 Pathogenesis of D+HUS following infection with Shiga-toxin producing *E. coli* (STEC).

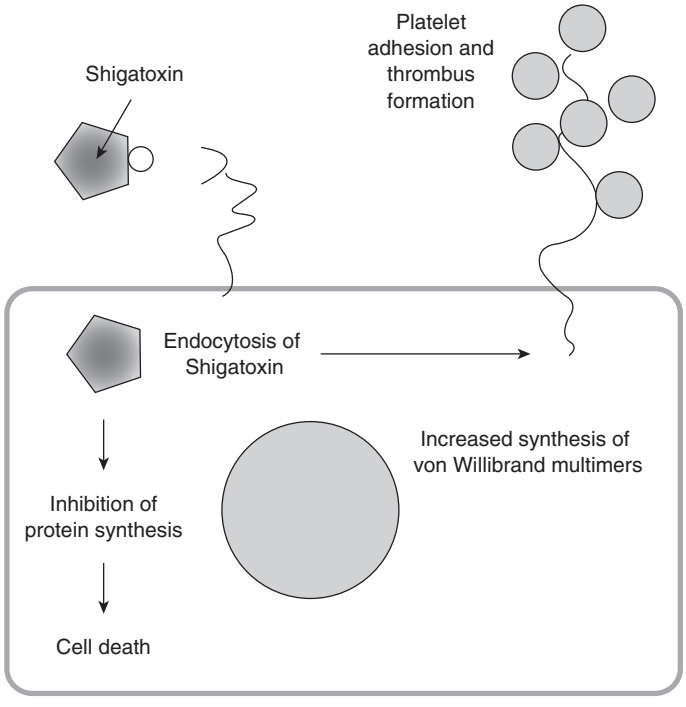

Figure 15.2 Cellular events in the pathogenesis of HUS by Shiga-toxin.

Complement protein factor H helps regulate alternative complement pathway activation by inhibiting the formation of the alternative C3-convertase and accelerating its decay as well as serving as a cofactor for the C3b-cleaving enzyme, factor I. In subjects with factor H dysfunction, complement deposition on endothelial cells, particularly in glomeruli, can lead to vascular injury and TMA.[44] Several different abnormalities of factor H function and quantity have been described in subjects with familial and/or recurrent HUS.[42] Other defects in complement regulation such as reduced expression of Membrane Cofactor Protein (CD46) have been described in some cases of familial HUS.[45,46]

Thrombotic thrombocytopenic purpura

The role played by vWF in the pathogenesis of TTP has now been understood more clearly. Most of the vWF synthesized by the endothelial cells is in a multimeric form that is cleaved by a metalloprotease enzyme in plasma known as *a d*isintegrin *a*nd *m*etalloprotease with *t*hrombos*p*ondin-1-like domains (ADAMTS 13). In the absence of ADAMTS 13 enzyme activity in plasma, the plasma multimers of vWF accumulate and promote platelet aggregation and formation of thrombi in the vascular tree (Figure 15.3). These thrombi usually lack fibrin and are composed mostly of platelet aggregations.

TTP may be seen in subjects with congenital absence of vWF-cleaving protease enzyme (ADAMTS 13) activity or with an acquired IgG antibody directed against ADAMTS 13.[47] Several new defects in vWF generation and regulation have now been described in individuals with recurrent TTP.[48,49]

Pathology

Irrespective of the underlying etiology of HUS, the classic pathologic lesions consist of endothelial cell injury and small-vessel thrombosis.[12] The morphologic findings of renal injury in HUS consist of:

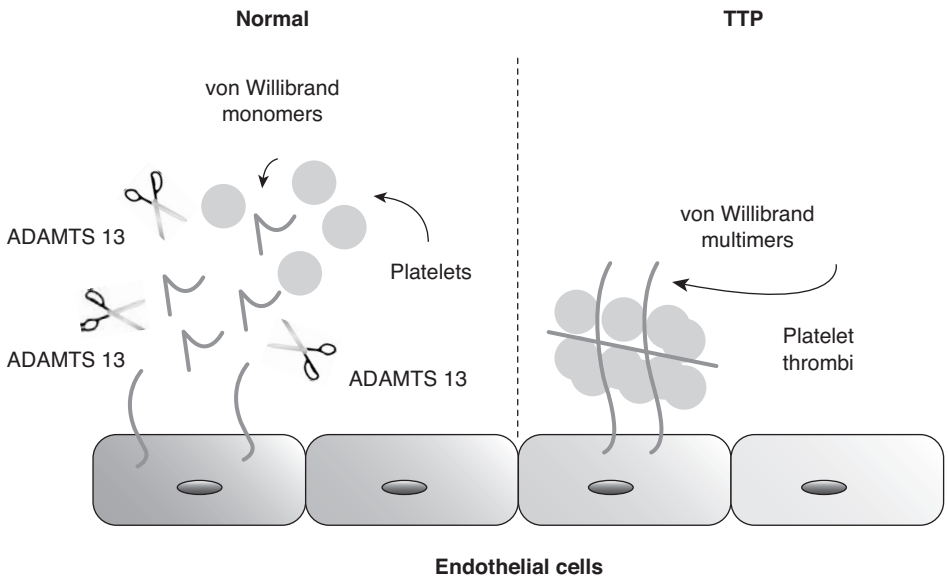

Figure 15.3 Pathogenesis of thrombotic thrombocytopenic purpura (TTP). Absence or inactivation of the protease ADAMTS 13 leads to accumulation of von Willibrand factor multimers in plasma, which promotes adherence of platelets to initiate thrombosis in microcirculation.

- glomerular, arteriolar, and interlobular arterial endothelial cell injury and thrombosis, leading to further ischemic injury
- signs of tubular cell injury and acute tubular necrosis (ATN).[49]

Glomerular thrombi with loss of open glomerular capillaries and thrombosis in interlobular arteries characterize HUS (Figure 15.4). The extent of ATN can be variable and may be prominent in some children. By electron microscopy, the earliest signs of injury consist of endothelial cell swelling, vacuolization, and separation of the endothelial cell from the basement membrane with 'fluffy' and fibrillar material and platelet fragments appearing under the separated endothelial cells. Later, mesangial matrix and cell expansion, endothelial cell necrosis, and small- and larger-vessel occlusion with platelet and fibrin thrombi are evident. By immunofluorescence microscopy, positive staining for fibrinogen, C3, and IgM is present in the vascular lesions.[50] Although HUS may be triggered by very different causes, the combination of endothelial cell injury and small-vessel thrombosis (TMA) is characteristic of all forms of HUS.[7]

Clinical presentation

Prodrome

Signs of GI illness characterized by abdominal pain, vomiting, and diarrhea precede the onset of HUS in D+ disease. In some cases, the GI manifestations may be minimal. More commonly, the diarrhea is pronounced and bloody. Severe cases may resemble ulcerative colitis. Some children present with signs of an acute abdomen, and the clinical findings may resemble appendicitis or intussusception.[51,52] In severe cases, intussusception or intestinal perforation may occur due to extensive intestinal injury.

In D– HUS or atypical HUS, GI symptoms are not seen. Most of these children present with a history of a prodromal respiratory illness, such as otitis, sinusitis, or pneumonia, which may still be present at the time of recognition of HUS.[39]

Onset

Anorexia, weakness, pallor, and jaundice are the presenting symptoms in many children with HUS. These manifestations may reflect the development of profound anemia as a result of microangiopathic hemolysis. As thrombocytopenia becomes more significant, bleeding, purpura, or petechiae may develop.

Oliguria and/or hematuria are the first manifestations of renal involvement in these patients. These manifestations may evolve over hours to a few days, depending on the severity of the disease. In many patients, oliguria may be initially interpreted as being the result of dehydration and prerenal azotemia. Progressive renal injury results in anuria. As acute renal insufficiency develops, fluid retention, edema, hypertension, and electrolyte disturbances may occur. Hyponatremia due to fluid overload (dilutional hyponatremia), high anion gap metabolic acidosis, and hyperkalemia may be seen at initial presentation in some patients. In other patients, these metabolic abnormalities develop subsequently.

Central nervous system symptoms, such as lethargy, irritability, seizures, cortical blindness, paresis, and coma occur in up to 30% of affected children.[53] Complications of renal insufficiency, such as hypertension, electrolyte disturbances, and uremia, may contribute to the CNS (central nervous system) symptoms. Evidence of other significant organ system damage

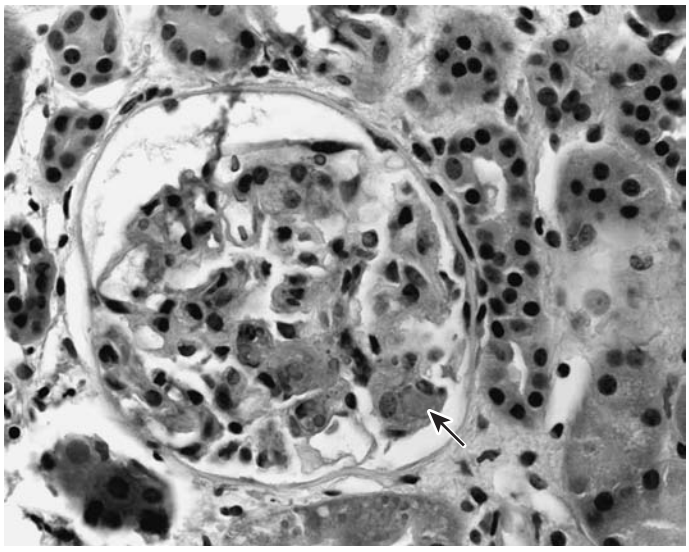

Figure 15.4 Renal biopsy showing a glomerulus from a child with postdiarrheal HUS. Arrow shows a glomerular capillary thrombus.

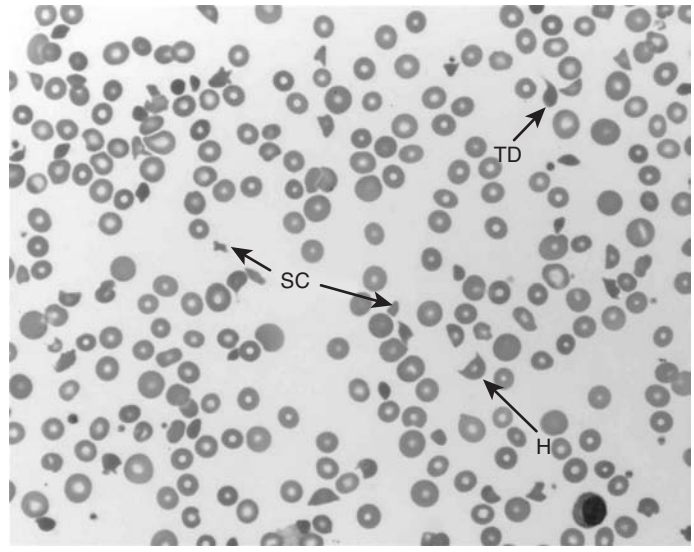

Figure 15.5 Peripheral smear from a child with HUS demonstrating evidence of microangiopathic hemolysis. Red blood cells (RBCs) and schistocytes: SC, schistocytes: H, helmet RBCs, TD, teardrop RBCs.

in HUS may become evident as the condition progresses.[54,55] Signs of muscle weakness or evidence of liver injury may develop. In some children, pancreatic injury can lead to hyperglycemia due to decreased insulin production.[56]

Evaluation and diagnosis

Urinalysis

Laboratory findings include multiple abnormal blood and urine tests. The urinalysis typically demonstrates hematuria, proteinuria, and cellular casts, although early in the course hematuria may be the only abnormality.

Hematologic profile

All patients have evidence of microangiopathic hemolytic anemia with low hemoglobin, and the peripheral smear shows evidence of RBC damage such as burr cells, schistocytes (fragmented RBCs) and tear drop cells, (Figure 15.5).[55] Thrombocytopenia with evidence of diminished numbers of new large platelets and a high mean platelet volume is generally seen, but platelet numbers may be low normal early in the course of the disease. Platelet count can drop to as low as 5000/mm^3. The reticulocyte count is typically elevated in response to intravascular hemolysis, although, as renal insufficiency develops, the reticulocyte count will be low. The leukocyte count is often elevated early in the course of HUS.[57] The direct and indirect Coombs tests are normal. The haptoglobin is low and indirect bilirubin high. Plasma lactate dehydrogenase (LDH) is high due to RBC lysis. The prothrombin and partial thromboplastin times are normal.

Shiga toxin assay

Although not commercially available yet, newer diagnostic methods, such as detection of Stx in stool, or Stx on the surface of circulating neutrophils, offer promise of more rapid detection of Stx-mediated HUS in the future.[58,59]

Renal function

The degree of renal insufficiency may be quite variable but usually manifests itself over 5–7 days after first evidence of renal involvement.[60] Laboratory evidence of acute renal failure is noted in more severely affected patients, including elevated blood urea nitrogen (BUN) and creatinine, hyperkalemia, metabolic acidosis, hypocalcemia, hyperphosphatemia, and hyperuricemia.

Diagnostic criteria

Diagnostic criteria for HUS include evidence of:

- microangiopathic hemolytic anemia
- thrombocytopenia
- signs of renal dysfunction.

Investigation of other causes of microangiopathic hemolytic anemia with renal disease (see Table 15.1) should be undertaken in all affected children. Renal biopsy is not necessary to confirm the diagnosis in most cases of HUS but may be indispensable in atypical cases.

For children with atypical HUS, D– HUS, or familial or recurrent HUS, careful consideration of these unusual etiologies must be entertained.[61] For children with recurrent or familial HUS, complement (C3, C4, C1q) and factor H levels should be obtained.[42,44]

Thrombotic thrombocytopenic purpura

If TTP is a diagnostic consideration, assays of ADAMTS 13 activity and antibodies directed to ADAMTS 13 are now commercially available and should be obtained.[47]

Other organ dysfunction

Other less-frequent laboratory findings, typically seen in more severely affected patients, include elevations of liver enzymes, creatine kinase, amylase, and lipase. For patients with pregnancy-associated HUS or HUS seen with medications, vasculitides, or other secondary disorders, the diagnosis is usually not difficult to establish.

Management

Most children with infectious or idiopathic HUS recover spontaneously with appropriate supportive care and management of acute renal failure.

Antibiotic use

Antibiotic therapy is not indicated in D+HUS or idiopathic HUS and has been associated with worse outcome in a few series.[31] Often, in D+HUS, by the time the child presents with signs of HUS, the diarrheal illness is resolving and stool cultures are often negative.

Intravascular volume

A recent study confirmed the earlier clinical observation that judicious volume expansion early in the course of HUS may attenuate the degree of renal impairment, and this approach should now be considered early in the support of the child with HUS.[62] Serum albumin is often low in these children and replacement with intravenous albumin may be useful; however, no clinical study supportive of this intervention has been reported.[63] Most importantly, once acute renal failure and oliguria have set in, fluid balance needs to be maintained with judicious use of intravenous and oral fluid intake, in order to avoid fluid overload and associated complications.

Anemia and thrombocytopenia

Treatment of anemia with judicious RBC transfusions is usually directed to keep the hemoglobin >8.0 mg/dl to avoid severe complications of anemia. During the latter stages of severe HUS with renal insufficiency, erythropoietin administration may be useful to maintain the hemoglobin count. While active microangiopathic damage is present, platelet transfusions do not provide prolonged improvement in the platelet count. Platelet transfusions might even worsen the TMA process.[64] Platelet transfusions are therefore not necessary in most patients, except in those with active bleeding from thrombocytopenia or who require surgical interventions (e.g. catheter placement, abdominal procedures).

Acute renal failure

Management of acute oliguric renal failure requires:

- strict attention to fluid balance[62]
- treatment of hypertension
- correction of metabolic disturbances such as hyperkalemia, metabolic acidosis, hypocalcemia, and hyperphosphatemia.[60]

The literature suggests that many clinicians consider peritoneal dialysis (PD) to be the modality of choice in most young children.[69] However, there are no randomized outcome data addressing this point, and some centers employ hemodialysis or continuous renal replacement therapy (CRRT).[60] When dialysis is required, it is generally needed for 5–7 days, although some patients have recovered after more than 1 month of dialysis support, albeit with evidence of some chronic renal insufficiency.

For all subjects with HUS, provision of adequate nutrition is important and may require TPN until the GI tract has recovered. Supportive care, and in particular early initiation of dialysis for severely affected children, has been the only therapy of proven value.

Other therapies

For D+HUS, other therapies such as antibiotics,[65] intravenous streptokinase,[66] plasma infusions,[67] plasmapheresis,[68] intravenous γ-globulin,[69] Stx-binding antitoxins,[70] and corticosteroids[71] have been shown to have no impact on outcome. In some cases of familial or recurrent HUS, plasma infusions and/or plasma exchange may be useful.[65]

Preventing hemolytic uremic syndrome

Prevention strategies are most useful to minimize exposure to STEC and include improved meat processing, food handling, and preparation.[72] Simple measures, like hand- and food-washing as well as avoidance of ingestion of raw and rare beef, remain effective strategies for prevention of acquisition of STEC infections and HUS.[2] In particular, ground beef must be cooked thoroughly because the pathogenic bacteria have been relocated to the inside of a hamburger patty, whereas they are more likely to be on the outside of whole cuts of beef.

Complications and prognosis

Organ dysfunction in acute illness

Complications may result from vascular thrombosis and infarction of the CNS (lethargy, coma, seizures, stroke),[73] myocardium (infarction, congestive heart failure),[74,75] GI tract (colonic perforation or stricture),[24,76] and/or pancreas (diabetes mellitus).[56] Such manifestations are usually seen in patients with severe disease. Prolonged anuria, need for dialysis, and evidence of non-renal organ system involvement are associated with worse prognosis.[77]

Mortality

Death still occurs in 2–5% of children with infectious or idiopathic HUS and is more common in association with evidence of non-renal organ system injury.[55,78] With good acute renal failure support, mortality is more commonly ascribed to severe non-renal complications. Older age at onset of D+ HUS has been related to worse outcome in some but not all studies.[11,79,80] In a large retrospective HUS series from Italy, absence of diarrheal prodrome and lack of defined STEC infection carried a worse prognosis.[11]

Chronic kidney disease and hypertension

Evidence of chronic renal damage (proteinuria, hypertension, and/or renal insufficiency) may be seen in up to 30–50% of children who recover from HUS. The incidence of long-term renal sequelae varies from 35 to 39% in several good long-term follow-up studies.[11,77,81] End-stage renal disease (ESRD) has been seen in 10–15% of survivors in studies with follow-up to 25 years.[82,83]

Significant hypertension may be present after recovery from HUS and may require multiple medications for control. In some children, initial renal recovery may be almost complete but hypertension and chronic renal insufficiency may ensue later and lead to progressive renal insufficiency over time.[83]

Long-term follow-up for children with any evidence of chronic renal sequelae is essential. In general, children without any evidence of proteinuria, hypertension, decreased GFR (glomerular filtration rate), or abnormal renal ultrasound at 1 year following HUS do not develop long-term sequelae at 5 years follow-up.[84] Although less frequent, the incidence of long-term sequelae and ESRD has been reported to be higher in children with *S. pneumoniae*-related HUS.[85]

For the 10–15% of D+HUS survivors who suffer progressive renal failure, renal transplantation can be offered without any concerns about recurrence of HUS.[86] In cases of atypical HUS, recurrence in the renal transplant may occur and lead to significant allograft compromise or loss.[87]

Clinical case

A 19-month-old Caucasian boy was admitted from the emergency department with a 5-day history of low-grade fever, anorexia, and watery diarrhea. His parents reported eating at a barbecue 2 days before his GI symptoms started. On the day of admission, his stools were streaked with blood. In the emergency department he was noted to be pale, fatigued, and slightly dehydrated. He had intermittent abdominal colic and vomited once.

Initial laboratory studies included urianalysis with blood and protein measurements: Hb, 11.0 mg/dl; WBCs 22 400/mm^3; platelets, 177 000/mm^3. The boy's reticulocyte count was 5.6%, with LDH 4980 U/L. The serum creatinine was 1.0 mg/dl; BUN, 34 mg/dl; sodium, 134 mEq/L; potassium, 3.8 mEq/L; HCO_3, 18 mEq/L; Cl, 98 mEq/L; calcium, 8.8 mg/dl; phosphorus, 4.8 mg/dl; albumin 2.8 mg/dl; liver transaminases, amylase, and lipase were normal; CK was elevated, at 448 U/L. Bacterial stool cultures were sent. The stool was positive for fecal WBCs. Intravenous hydration was initiated.

On hospital day 2 the boy's hemoglobin was 8.3 mg/dl and platelets 74 000/mm^3. His stool culture was positive for *E. coli* O157:H7. A rectal prolapse needed to be reduced with use of sedation. His serum creatinine was 1.8 mg/dl and he had <0.5 ml/kg/h urine output. A PD catheter was inserted on hospital day 3 because of anuria and progressive azotemia. Severe hypertension was treated with short-acting and long-acting calcium channel blockers. He was started on intravenous (IV) erythropoietin for anemia but required two RBC transfusions to maintain his hemoglobin >8.0 mg/dl during the first week on PD. TPN was initiated on hospital day 5 and he subsequently required insulin therapy for control of hyperglycemia. At that time, his lipase was elevated, at 1266 mg/dl.

On hospital day 6, on the third day after starting PD, hydrothorax was noted and PD was discontinued for 2 days. Hydrothorax did not reoccur on restarting PD. His TPN and insulin therapy were able to be discontinued on hospital day 22 after resumption of improved oral intake. PD was performed for 29 days before substantial urine output returned and PD was able to be discontinued.

By hospital day 35, the boy's urine output was good, oral intake was good, and serum creatinine was 1.2 mg/dl. His PD catheter was removed on day 36, and he was discharged to home the following day on enalapril 1.25 mg bid.

Comment

This boy's initial presentation was quite typical for D+HUS. His initial CBC (complete blood count) had only mild anemia and an elevated WBC (white blood cell count). His thrombocytopenia, anemia, and renal dysfunction became more impressive over the next few days and dialysis was started once severe oliguria was noted in this setting. He did not receive antibiotic therapy. RBC transfusions and erythropoietin were employed; platelet transfusions were not given. His blood pressure was difficult to manage, although less of a problem over time. He still required antihypertensive therapy at the time of discharge and his renal function never returned to normal (serum creatinine 0.9 mg/dl at 6 months after resolution of active HUS).

Unfortunately the boy's long-term outcome was characteristic of the subset of children with HUS who do not experience a complete recovery from the acute HUS injury and stresses the need for continued follow-up of affected patients. Three years after his recovery, further renal impairment was noted with no evidence of active HUS. His hypertension became more problematic and he developed progressive renal insufficiency. He received a successful renal transplant 14 years after his recovery from acute HUS and is now doing well, with no signs of recurrent HUS.

Concluding remarks

HUS is a clinical syndrome characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal injury. Although there are many distinct causes of HUS in children, up to 90% of cases are related to GI infection (D+HUS) with Shiga toxin-producing *E. coli* or *Shigella*. Supportive care is essential to good outcome, and the course and outcome is related to the underlying cause. With D+HUS, mortality is now <5% but a large number of survivors exhibit signs of proteinuria, hypertension, or renal insufficiency and deserve continued follow-up. Children with D− HUS are a more heterogeneous group; management strategies are not well defined and outcome is less favorable in this group.

Improved public health prevention strategies remain the best option to decrease the frequency of D+HUS in children. For children with established STEC colitis, passive immunity to Stx toxins or administration of Stx receptor analogues offer an opportunity to minimize disease severity. Unfortunately such efforts remain to be proven to be effective in affected children and all such efforts are limited by the ability to detect STEC colitis early enough to be able to intervene. HUS continues to be a challenge in terms of prevention; even for severely affected children, appropriate supportive management of acute renal insufficiency and non-renal complications can provide a good outcome.

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16 Kidney in systemic lupus erythematosus and vasculitis

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The highly vascular nature of the kidneys explains their frequent involvement in inflammatory vascular diseases. The fundamental pathologic process in *vasculitis* is a neutrophilic inflammatory infiltration of the blood vessel wall and concomitant effects of inflammatory mediators, with acute and chronic changes in the blood vessels that evolve over time. Identification of vasculitis in a patient may be difficult because of varied manifestations, overlapping clinicopathologic features, and heterogeneity in etiologies. Vasculitides, because of the different caliber vessels involved, may result in necrosis of the glomerular capillaries (necrotizing glomerulonephritis), or may compromise the entire kidney as a functional unit in medium- or large-vessel vasculitis.

The classification of renal vasculitis may reflect primary versus secondary etiologies, immune complex associated versus non-immune complex mediated (pauci-immune), size of the vessel affected, or type of inflammatory injury.[1] The Chapel Hill Nomenclature System divides vasculitis into three groups, depending on the size of the affected vessels (Table 16.1).[2] Although some overlap does occur, the large and medium vessel vasculitides, such as polyarteritis nodosa or Takayasu's arteritis, affect the kidney less frequently. Medium- and large-vessel vasculitis affecting kidney typically manifests renovascular hypertension, vascular thrombosis, and vascular rupture. In contrast, the small-vessel vasculitides predominately affect arterioles, capillaries, and venules. Consequently, they result in glomerulonephritis by affecting the glomerular capillaries. Such vascular disease often leads to renal insufficiency, and end-stage renal disease (ESRD) can occur. Hypertension is also commonly seen with the small-vessel diseases.

The pediatric nephrologist most often encounters patients with small-vessel vasculitides, such as Henoch–Schönlein purpura and systemic lupus erythematosus (SLE), and the much less common pauci-immune vasculitides. The systemic vasculitides can cause substantial morbidity by their effect on many organ systems as well as the kidney.[3] Henoch–Schönlein purpura, the most common form of systemic vasculitis in children, is discussed in Chapter 13. The primary focus of discussion in this chapter will be on other small-vessel vasculitides.

Table 16.1 Classification of the vasculitides by vessel size

Large-vessel vasculitis:
- Giant cell (temporal) arteritis
- Takayasu's arteritis

Medium-vessel vasculitis:
- Polyarteritis nodosa (classic polyarteritis nodosa)
- Kawasaki disease
- Cogan's syndrome

Small-vessel vasculitis (pauci-immune-mediated):
- Wegener's granulomatosis
- Churg–Strauss syndrome
- Microscopic polyangiitis (microscopic polyarteritis)

Small-vessel vasculitis (immune-mediated associated):
- Henoch–Schönlein purpura
- Systemic lupus erythematosus
- Rheumatoid vasculitis
- Anti-glomerular basement membrane disease
- Infection-induced vasculitis (i.e. hepatitis B and C)
- Cryoglobulinemic vasculitis
- Serum sickness vasculitis
- Hypocomplementemic urticarial vasculitis
- Behçet disease
- Post-organ transplant vasculitis
- IBD-associated vasculitis
- Malignancy-related vasculitis
- Scleroderma-associated vasculitis
- Dermatomyositis-associated vasculitis

Systemic lupus erythematosus

SLE is a common rheumatologic disease that is associated with significant morbidity and mortality in children.[4] It is an autoimmune chronic inflammatory systemic disease that has the potential to affect various organ systems, including the kidneys. SLE is a complex disease that is likely to result from a combination of an inherent susceptibility to an environmental exposure, as well as to a genetically determined abnormality of the immune system. Renal involvement is seen at onset in 28–100% of children, depending on the patient age and source of data.[5,6] When SLE nephritis is not part of the initial constellation, it is still likely to evolve and often becomes one of the most significant prognostic factors for long-term morbidity and mortality in a child with this disease.[5,7–10]

Epidemiology

SLE is significantly more common in females. The female to male ratio rises from 2:1 in prepubertal children, to 4.5:1 in adolescence, and finally to an approximate 10:1 in adults.[11] The prevalence of SLE in children is estimated as high as 10 per 100 000 individuals compared with an estimated prevalence in the general population of 50 per 100 000 when all ages are included.[12] Variations in the reported prevalence of SLE are likely to be related to referral bias, as well as to the ethnic make-up of the selected populations studied. For instance, the relative risk of SLE in non-white pubescent females compared with white pubescent females has been estimated to be 7 for Asian females, 4.5 for black females, and 3 for Hispanic females. An even higher relative risk is reported in a study of blacks in the United Kingdom.[13] The burden of this disease on African-American and Hispanic populations is further compounded by an increased severity, with worse prognosis.

Pathogenesis

The pathogenesis of SLE continues to be an area of active research. The origins of loss of the 'self'-recognition stems from a combination of T-cell and B-cell dysregulation, complement dysfunction, and culminates in a loss of tolerance of self. Normally, B cells that are able to recognize an individual's own antigens are tightly controlled and eliminated. In SLE, the failure of tolerance is manifest by the presence of autoantibodies to self-antigens such as DNA, nuclear proteins, and certain cytoplasmic proteins.[14] The stimulus for generation of these autoantibodies is probably fostered by a failure to effectively clear apoptotic debris containing nuclear proteins and chromatin.[15] These self-antigens are then recognized by abnormal self-reactive B cells. Through B-cell and T-cell cooperation, this results in B-cell activation and the creation of both effector and memory B cells. Effector B cells release IgG autoantibodies into the circulation, which form antigen–antibody complexes. These complexes accumulate in the small vessels of organs, where they stimulate local inflammation by activating complement pathways. Binding of Fc receptors leads to mast cell degranulation and local infiltration of macrophages and neutrophils ensues.

The genetic susceptibility to SLE is supported by the occurrence of familial aggregation, the disease concordance rate in twins, and the increased sibling risk.[16] The genetic contribution appears to involve multiple loci with small to modest individual effect. There are 8 significant susceptibility loci that have resulted from 9 separate genome-wide scans and 6 targeted scans.[17–24] Each of these has subsequently been confirmed in alternative cohorts.[19–21,23,25,26] Within these loci, several candidate genes have shown association with SLE. Among the most convincing candidates are three MHC haplotypes, PARP, C4, TNFA, PDCD1, CRP, PBX1, and the Fc receptors FCGR2A, FCGR2B, and FCGR3A. Polymorphisms in the FCGR3A gene reportedly confer a 1.2-fold increased risk for developing lupus nephritis in some populations.[27]

Because SLE may affect the vascular, glomerular, and tubulointerstitial compartment to differing degrees, the inflammatory disease in the kidney can present in a variety of histologic patterns. Glomerular involvement results from deposition of immune complexes, glomerular response, and injury resultant from antigen specificity and complement stimulation. The pathologic classification of lupus nephritis continues to evolve, with growing knowledge of its pathogenesis and therapeutic response. The significance of renal pathology in the management of SLE is reflected by recent reviews of the proposed pathologic classification of SLE nephritis in the nephrology literature.[28,29]

Pathology

The International Society of Nephrology and Renal Pathology Society (ISN/RPS) 2003 classifies lupus nephritis into six categories (Table 16.2). Class I lupus nephritis is minimal mesangial lupus nephritis. The glomeruli are normal by light microscopy, but there is evidence of renal involvement by immune complex deposition on immunofluorescence microscopy or electron microscopy (Figure 16.1). Class II lupus nephritis includes mesangioproliferative lesions by light microscopy (Figure 16.2). Class III focal proliferative lupus nephritis is defined as involving less than 50% of all glomeruli and is divided into active (A) and chronic (C) lesions. The active lesions include endocapillary hypercellularity, leukocyte infiltrates, karyorrhexis, necrosis, cellular crescents, and hyaline thrombi. The chronic lesions are characterized by sclerosis, adhesions, or fibrous crescents. Class IV diffuse proliferative lupus nephritis involves the same lesions as in class III, but with greater than 50% of all glomeruli affected with either active, chronic, or both (acute and chronic) findings (Figure 16.3). Additionally, class IV is subdivided into global (G), involving the entire affected glomerulus, or segmental (S), affecting less than half of the affected glomerulus (Figure 16.4). Class V lupus nephritis is membranous lupus nephritis, and is characterized by subepithelial deposits in the majority of capillary loops (Figure 16.5). Class V lupus nephritis may be coincident with class III and class IV lesions. Class VI sclerosing lupus nephritis is the end result

Table 16.2 Distribution of lupus nephritis lesions in children and adolescents from the Glomerular Disease Collaborative Network[a] patient registries

WHO Classification	Lesion	*N*=80	Percent
I	Mesangial immune complex	3	4
II	Mesangioproliferative	12	15
III	Focal proliferative	14	17
IV	Diffuse proliferative	43	54
V	Membranous	8	10
VI	Sclerosis	0	0

[a]Clinical Coordinating Center, University of North Carolina, Division of Nephrology and Hypertension, Chapel Hill NC.

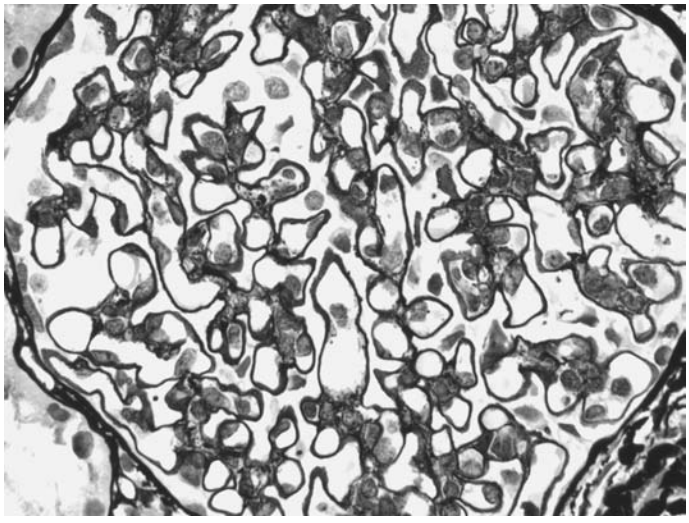

Figure 16.1 Class I (ISN/RPS 2003) minimal mesangial lupus glomerulonephritis. Glomeruli are normal by light microscopy, but are positive for immune complex deposition by immunofluorescence microscopy.

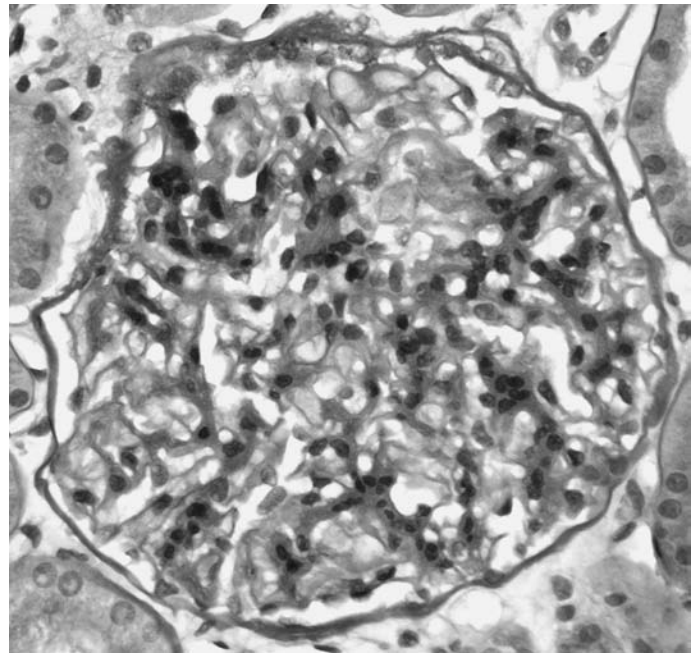

Figure 16.2 Class II (ISN/RPS 2003) mesangial proliferative lupus glomerulonephritis: only mesangial proliferation (>3 mesangial cells per mesangial area in a 3-μm section) with any degree of matrix expansion by light microscopy, positive immunofluorescence microscopy, and electron microscopy for immune complex deposition (original magnification: 200×, periodic acid–Schiff stain).

(chronic lesions) of renal lupus involvement, with >90% globally sclerotic glomeruli (Figure 16.6).

Clinical manifestations

SLE is often more acute and more severe when its onset is before the age of 16.[30,31] The aggregates of immune complexes in SLE can deposit throughout the body, many organ systems may be involved, and a broad spectrum of possible clinical presentations can result.[6,9,32] As the patient and the disease progress, additional organ system involvement can alter the individual patient's clinical presentation. Generalized symptoms of fever, fatigue, weight loss, and anorexia are common. Abdominal pain caused either by vasculitis or serositis occurs frequently in children with SLE. Rash occurs in over 50% of SLE patients, and alopecia is also frequent.[6,33,34] The musculoskeletal complaints, such as arthralgias, arthritis, myalgias, or myositis, occur in nearly 86% of children, with both large and small joints being affected similarly.[33] Pulmonary involvement occurs in more than 75% of children, and can manifest as pleuritis, dyspnea, and restrictive lung disease. Pericarditis and endocarditis are well-known clinical manifestations of cardiac involvement in pediatric SLE. Neuropsychiatric symptoms, typically attributable to central nervous system vasculitis, are frequent in the pediatric SLE and include headache, chorea, cranial nerve palsies, and psychiatric and behavioral problems. Hematologic abnormalities such as normochromic, normocytic anemia, hemolytic anemia, neutropenia, lymphopenia, and thrombocytopenia are common.

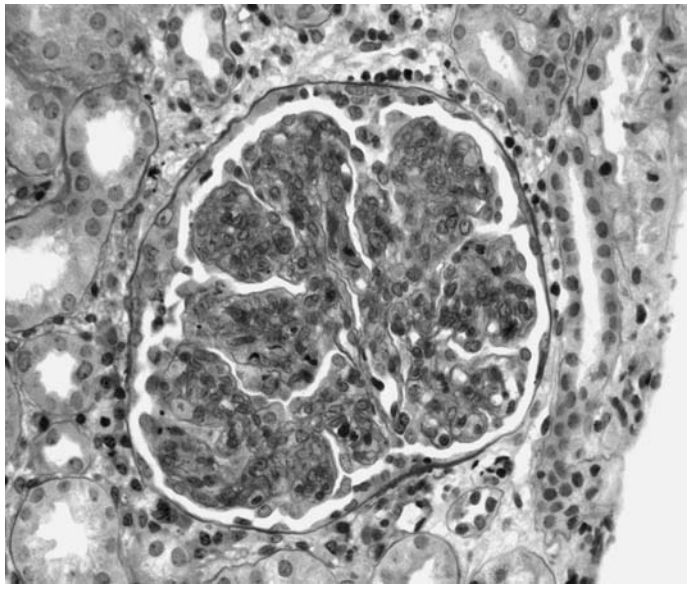

Figure 16.3 Class IV G (A) (ISN/RPS 2003) diffuse proliferative lupus glomerulonephritis. Class IV lesions involve greater than 50% of the total sampled glomeruli. The designation of G (global) is given to those cases with endocapillary hypercellularity involving ≥ 50% of the individual glomerular capillary tufts. The application of A, C, or combined (A and C) refers to the type of capillary tuft injury: active, chronic, or combined active and chronic injury. Class IV lesions have positive immune complex deposition by immunofluorescence microscopy and by electron microscopy. The active or chronic tubulointerstitial injury and vascular findings are reported separately.

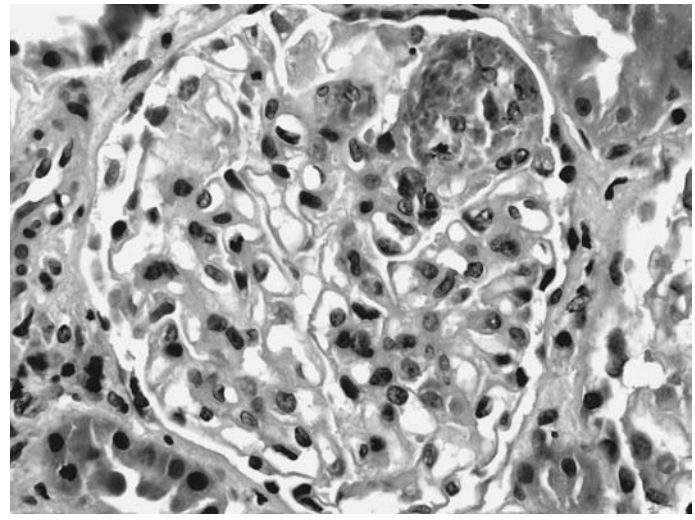

Figure 16.4 Class IV S (A) (ISN/RPS 2003) diffuse proliferative glomerulonephritis. Over 50% of the total sampled glomeruli (not shown) have glomerular capillary tuft injury. In the glomeruli from this case, the tuft injury is segmental (less than 50% of the individual glomeruli), and necrosis is seen at the 1 o'clock position. The lesion is an active lesion, and no chronic glomerular capillary tuft injury is apparent. The immunofluorescence microscopy and electron microscopy are also positive for immune complex deposition. If in a biopsy sample less than 50% of the glomeruli are involved, with the same injury as pictured, the designation would be ISN/RPS 2003 class III (A). The electron microscopy subendothelial immune complex type electron-dense deposits did not exceed half of the glomerular capillary walls examined. If there is extensive ultrastructural subendothelial immune complex deposition present, then the class designation is raised to class IV.

The initial presentation of SLE is typically seen due to extrarenal symptoms. Justification for initial and serial evaluation for renal vasculitis is supported by the observation that up to 80% of children with SLE develop nephritis over the course of their disease.[11] Clinically evident lupus nephritis may manifest a combination of hematuria, proteinuria, edema, diminished glomerular filtration rate (GFR), or hypertension. Abnormal urinary sediment consisting of cellular casts and sterile pyuria due to renal inflammation are frequently present. Renal tubular dysfunction may be present, and this can manifest as metabolic acidosis, normoglycemic glycosuria, and electrolyte imbalance. It is important for the pediatrician to recognize that the severity of renal involvement in SLE is not precisely gauged by clinical and laboratory findings, and that a renal biopsy may be necessary for assessing the severity of lupus nephritis and for guiding therapeutic decision making.

Evaluation and diagnosis

The diagnosis of lupus nephritis is most often made in a patient with other signs and symptoms of SLE. The clinical history and examination should prompt the screening for antinuclear antibodies (ANA). Autoantibodies are often present in the serum of SLE patients. These autoantibodies associate with their complementary antigen and form immune complexes that are either detected in the circulation, or are found as immune deposits in tissue biopsies. The immunofluorescent ANA screen allows for the detection of antibodies that bind an array of potential nuclear antigens such as DNA, RNA, and proteins. Although ANA are present in as many as 95% of SLE patients, it should be noted that as many as 30% of individuals with a positive screening ANA titer of 1:40 are healthy and without lupus.[35] The false-positive rate drops to 3% if the reported titer is 1:320. Additionally, since diseases other than SLE are associated with positive ANA test results, the predictive value of a positive test depends upon the test population. In patients with other rheumatic and collagen vascular diseases, a positive ANA may have only a 20–35% predictive value for SLE.[36] However, the negative predictive value, which is the probability of having SLE if the ANA test is negative, is less than 0.14%. Nonetheless, if the ANA is positive and SLE is suspected, anti-double-stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm) antibodies should be ordered. These antibodies are the most highly specific for systemic lupus erythematosus. Although anti-dsDNA and anti-Sm antibody specificity is much greater than the screening ANA, their sensitivity is much lower, being 40–90% and 5–30%, respectively.[11]

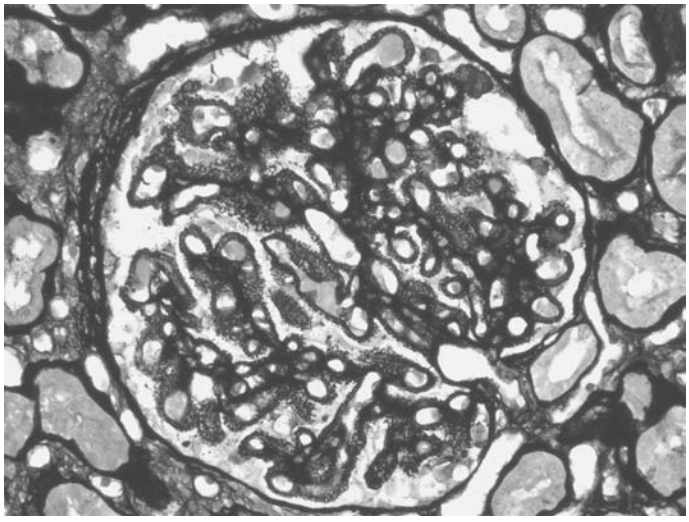

Figure 16.5 Class V (ISN/RPS 2003) membranous lupus glomerulonephritis. Light microscopy, immunofluorescence microscopy, and electron microscopy reveal subepithelial deposits, with global, segmental, or diffuse distribution. Associated mesangial alterations are frequently present. When a class V lesion has additional tuft abnormalities, then a designation of combined class V and III or IV is warranted, depending on the distribution of the additional lesions.

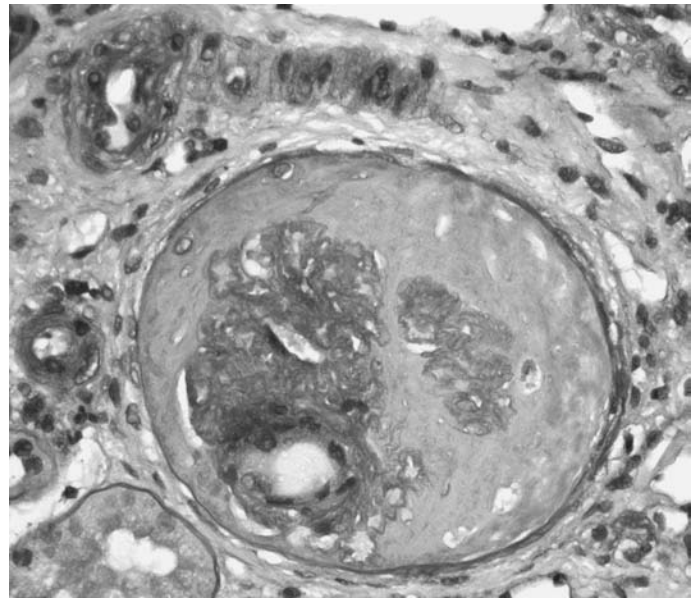

Figure 16.6 Class VI (ISN/RPS 2003) advanced sclerosis lupus glomerulonephritis. By light microscopy, there is greater than 90% global glomerular sclerosis without residual activity.

Antiphospholipid antibodies may occur in 29–87% of children with SLE.[37–40] The increased risk of thrombotic events in children with antiphospholipid antibodies is well known.[37,38]

The anti-DNA antibodies are the most highly associated autoantibodies in lupus nephritis. The pathogenicity of anti-DNA in this setting has been substantiated by three separate observations:

- anti-DNA levels tend to correlate with the relative activity of lupus nephritis[41–43]
- the anti-DNA antibody can be isolated from the glomeruli of the affected kidneys[44]
- nephritis can be induced in normal mice by administration of monoclonal anti-DNA antibodies.[45]

Lupus nephritis can be present in the absence of anti-DNA, suggesting additional or alternative mediators as well. Immune complexes of SLE can activate the classic complement pathway. Therefore, the detection of the consumption of complement may also be useful in supporting the diagnosis of lupus nephritis. Hypocomplementemia is found at presentation in more than three-quarters of SLE patients and is more common with lupus nephritis.[46,47] In patients with a genetic C4 or C1q deficiency, these specific complement components do not normalize with control of the disease.

Lupus nephritis patients have varying degrees of renal dysfunction. The most useful laboratory studies for the diagnosis of lupus nephritis are the clinical markers of nephritis, serologic markers of autoimmunity as discussed above, and the renal biopsy. Additional laboratory evaluation includes a complete blood count (CBC), with differential count to screen for anemia, thrombocytopenia, and leukopenia. Blood urea nitrogen (BUN) and creatinine can be used to suggest the degree of renal impairment. Serum electrolytes evaluate for tubular dysfunction. Serum albumin is often used to further define the impact of proteinuria. And, finally, a urinalysis with microscopy and quantification of urine protein excretion aid in determining the severity of renal disease.

Diffuse lupus glomerulonephritis (class IV) is seen in 20–50% of all children presenting with SLE who are subjected to renal biopsy,[48] with a higher incidence in African-American and Hispanic children. In the Glomerular Disease Collaborative Network patient registry, with a predominantly African-American patient group, 54% of children and adolescents biopsied for diagnosis and classification of lupus nephritis had diffuse lupus glomerulonephritis (class IV) (see Table 16.2). Just as the overall systemic disease may wax and wane, and involve new systems, lupus nephritis may recur or change to a different class over time.

Differential diagnosis

The differential diagnosis for a patient suspected of SLE nephritis can be narrowed, based on the presence or absence of other clinical and objective laboratory findings. Henoch–Schönlein purpura (HSP) can present with joint pain, systemic symptoms, nephritis, and a purpuric rash. HSP is, however, characterized by an absence of antinuclear antibodies. The renal biopsy in HSP demonstrates a dominant IgA staining pattern on immunofluorescence, which is not seen in SLE.

Peri-infectious syndromes may also masquerade as SLE, especially if both nephritis and arthritis are clinically present. Unfortunately, the ANA may also be positive in this setting, complicating the picture. If the kidney biopsy does not provide the diagnosis, the postulated infection is treated. Close follow-up is warranted, and the aggressive immunosuppressive regimen required for proliferative lupus nephritis lesions is reserved for a confirmed diagnosis.

ANA positivity can be seen in a number of other rheumatologic diseases that may involve the kidney, particularly in mixed connective tissue disease and rheumatoid arthritis (RA). The diagnosis of RA may be established by radiologic evaluation of the affected joint(s), which may show erosions and deforming arthritis. Therefore, presentation with renal disease, a positive ANA, and deforming arthritis is suggestive of RA. Finally, thrombocytic thrombocytopenia purpura (TTP), which may occur in the setting of SLE, can lead to significant renal pathology with symptoms of oligo-anuria, acute renal failure, hemolytic anemia, and thrombocytopenia far exceeding those expected with the classic lupus nephritis lesion. Since TTP does not respond to the therapy used to treat lupus nephritis, it is crucial that this disorder is identified and treated appropriately.

Treatment strategies

The therapy for lupus nephritis is usually based on the histopathologic classification of renal disease. Class I and class II renal lesions are mild histologic lesions that tend to respond to corticosteroids alone. In this circumstance, careful surveillance is required to ensure that a transformation to a more severe kidney lesion is identified and treated early. Focal proliferative glomerulonephritis (class III) and diffuse proliferative lupus nephritis (class IV) require additional immunosuppressive therapy to lessen the morbidity and mortality of the disease. These two groups of patients are at significant risk of progression to ESRD if the nephritis is uncontrolled.[49] Additional indicators of the need for aggressive therapy for class III lupus nephritis are patients with an elevated creatinine level at the time of renal biopsy, severe nephritic syndrome, crescent formation on biopsy, severe tubulointerstitial disease, and evidence of vasculitis.[50]

Because of the risk of progression and recurrence of the disease, therapy for proliferative lupus nephritis is structured into induction and maintenance phases. The most common induction regimens for proliferative lupus nephritis include a combination of corticosteroids and cyclophosphamide. The duration of cyclophosphamide is typically 3 months orally, or 6 months given intravenously (IV). Extension of therapy is based on lack of control of nephritis based on clinical parameters, or by repeat kidney biopsy. Maintenance-phase therapy with quarterly IV cyclophosphamide, daily azathioprine, or, most recently, daily mycophenolate mofetil, has been prescribed for a 1- to 2-year duration.

The NIH (National Institutes of Health) trials first established the superiority of incorporating cyclophosphamide in addition to corticosteroids, over monotherapy with corticosteroids alone, in prolonging renal survival. The NIH regimen, which included 2 years of cyclophosphamide exposure, improved renal survival, but resulted in significantly higher morbidity for the combined cyclophosphamide and corticosteroid group.[51–56] Concerns regarding complications, rate of infection, decreased fertility, and risk of other drug toxicities have prompted clinicians to consider shortened or alternative immunosuppressive strategies. The Euro-Lupus Nephritis Trial (ELNT) has supported reducing the high dose of immunosuppressives and shortening the course of cyclophosphamide.[57] In ELNT, 90 adult patients with proliferative lupus nephritis were randomly assigned either to 6 pulses of fixed dose IV cyclophosphamide (500 mg) given every 2 weeks to a cumulative dose of 3g or to 6 monthly doses of IV cyclophosphamide for induction, plus 2 quarterly pulses for the maintenance-phase therapy. All patients received corticosteroids. At 41 months of follow-up, there were no differences in treatment failure or renal flare.

Additional attempts to reduce the cumulative dose of cyclophosphamide have utilized alternate immunosuppressive agents following the initial induction of remission by cyclophosphamide. Two recent studies suggest that drugs other than cyclophosphamide may induce remissions. These preliminary studies using mycophenolate mofetil to induce remission in active lupus nephritis patients (class III, IV, or V) compared with IV cyclophosphamide found a greater number of complete and partial remissions was achieved in the mycophenolate group.[58] In this induction-phase study, severe infections occurred only in the cyclophosphamide group. During a relatively short follow-up phase, the mycophenolate mofetil-treated patients had similar plasma creatinine concentrations, urinary protein, and activity of urine sediment, suggesting that mycophenolate mofetil may be as good as or better than the current standard of cyclophosphamide for induction therapy. However, a greater relapse rate in the mycophenolate mofetil induction patients (15%) compared with cyclophosphamide (11%) has been observed.[58]

In North America, in a maintenance-phase study, 59 adults with lupus nephritis (12 focal proliferative, 46 diffuse proliferative, and 1 membranous lupus) were treated with an induction regimen of 4–7 consecutive monthly IV cyclophosphamide doses, plus corticosteroids.[59] Following this regimen, a maintenance phase was started in which patients were randomly assigned to 3 years of azathioprine (1–3 mg/kg/day), mycophenolate mofetil (500–3000 mg/day) or IV cyclophosphamide (0.5–1.0 g/m^2 every 3 months). Outcomes in the azathioprine and mycophenolate mofetil maintenance group were favorable, as the incidence of chronic renal failure, adverse effects, and mortality were significantly reduced compared with the cyclophosphamide arm.

A number of additional therapies are being evaluated in resistant lupus nephritis. Rituximab (Rituxan) is an antineoplastic humanized monoclonal antibody that causes a decrease in the B-lymphocyte population. Since B cells are the progenitors of the antibody-producing plasma cells, their modulation

may play a significant role in the control of an antigen–antibody-driven disease. This drug has shown some promise in pilot studies of patients with lupus nephritis who were resistant to treatment with combinations of other immunosuppressive agents. Plasmapheresis has not been proven to be beneficial in lupus nephritis, but is typically prescribed in the setting of TTP.

Limited randomized data exist for the application of each of the above treatment modes in children. In general, pediatric nephrologists extrapolate from the adult patient literature to build treatment plans that reflect the best of randomized controlled data combined with experience. Toward that end, proliferative lupus nephritis lesions are approached with combination regimens. Corticosteroids and cyclophosphamide are often used, although the length of therapy is variable. Alternative induction regimens with agents such as mycophenolate mofetil and corticosteroids are used because they offer fewer side effects, but long-term renal survival data are lacking. Similar to azathioprine, mycophenolate mofetil has also gained a place in the maintenance phase of therapy for lupus nephritis lesions in children.

Membranous lupus nephritis has the potential for morbidity secondary to uncontrolled nephrotic syndrome and, less commonly, chronic renal insufficiency or failure. Treatment of this disorder is not as clearly defined as that for the proliferative lesions, and no randomized trials have been published. Treatment regimens have included supportive therapy with angiotensin-converting enzyme (ACE) inhibition alone or in combination with an additional immunosuppressive agent, including cyclosporine, azathioprine, mycophenolate mofetil, cyclophosphamide, or chlorambucil with or without corticosteroids.[60] The low risk of renal failure from membranous lupus nephritis (approx 5%) has encouraged a less-aggressive approach to management compared with the proliferative lupus nephritis lesions. However, the significant morbidity associated with uncontrolled nephrotic syndrome, including the potential for accelerated atherosclerosis, thrombosis, and infections, supports intervention.

Outcome

The complications resulting from lupus nephritis can be divided into two main categories:

- those that result from the chronic disease itself
- those that are related to the toxicity of therapeutic regimens.

In general, lupus nephritis is a relapsing and remitting disease, and ESRD occurs in as many as 20% of lupus nephritis patients.[61,62] The African-American population is considered to be at high risk for ESRD. Infection is a major cause of morbidity in the pediatric SLE patient, presumably resulting from hypocomplementemia and the decreased number and function of neutrophils. This is further complicated by the therapeutic use of immunosuppressive agents. Long-term follow-up of one NIH trial documented that 26% of patients taking cyclophosphamide developed a serious bacterial infection.[54] This number increased to 32% when steroids were added to the patient's regimen, and is one of the primary driving forces behind defining newer, less-immunosuppressive, yet effective therapies.

Infertility is a significant concern associated with therapy for lupus nephritis. Boumpas et al reported that 51% of women over the age of 30 are at risk of developing ovarian failure after treatment with cyclophosphamide.[63] The concomitant use of a gonadotropin-releasing hormone agonist such as leuprolide acetate has been suggested to induce a state of ovarian protection from the cyclophosphamide effects.[64] Bladder cancer and lymphoproliferative disorders have been documented following cyclophosphamide use. In children and adolescents, the incidence of these side effects from the currently low-dose cyclophosphamide regimens is unknown.

Steroid therapy alone, or in conjunction with other immunosuppressives, is associated with further complications. Avascular necrosis has been reported in as many as 30% of patients treated with significant methylprednisolone exposure. Cataracts without visual impairment are a well-documented morbidity associated with significant steroid use. Hyperglycemia, short stature obesity, and osteopenia may also be caused by intense or prolonged courses of corticosteroids.

Clinical case 1

A 15-year-old black female presented with a history of fatigue, joint swelling, and anorexia. She denied fever. She had had an unintended 6 lb (2.7 kg) weight loss in the last 2 months. She reported a new symptom of shortness of breath while in dance classes, and denied facial or extremity edema. She had had bilateral wrist and knee pain and swelling for approximately 2 months. She felt her eyes were sensitive to light and reported a faint pink facial rash on her cheeks several times over the last 2 months. She denied mouth ulcers but had an increased hair loss over the last 3 months. Past medical history was significant for gastroesophageal reflux. Family history was significant for SLE in an aunt.

Urinalysis revealed a specific gravity of 1.022; 3+ protein; 3+ blood; 25–30 RBCs/hpf (red blood cells per high-power field); 5–10 WBCs/hpf (white blood cells per high-power field); 5–10 RBC casts; urine protein/creatinine ratio, 5.2; BUN, 31 mg/dl; creatinine, 2.8 mg/dl; albumin, 3.0 g/dl; WBC count, 4200/mm^3; hematocrit, 28%; platelet count, 100 000/mm^3; ANA, 1:1280; anti-dsDNA, 1:32; complement C3, 48 mg/dl (normal 83–177 mg/dl); complement C4, 14 mg/dl (normal 15–45); erythrocyte sedimention rate (ESR), 32 mm/h; and C-reactive protein (CRP), 4 mg/dl (normal < 1.0).

Renal biopsy showed that over 50% of glomeruli have evidence of endocapillary hypercellularity (Figure 16.7). Almost half of the affected glomeruli have cellular crescent formation, with distortion of Bowman capsule. Moderate interstitial edema and some tubules contain prominent RBC casts. There are scattered interstitial mononuclear leukocytes. The arteries and arterioles have no sclerotic or inflammatory changes. On

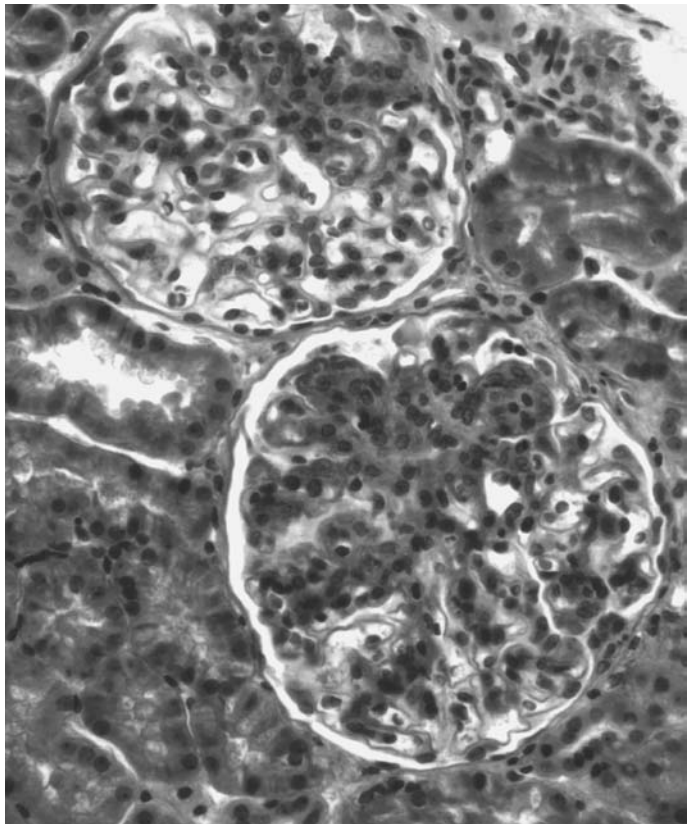

Figure 16.7 Clinical case 1. The glomerulus on the right has endocapillary hypercellularity in the 8–1 o'clock position. In contrast, other capillary loops are open with luminal red blood cells present.

immunofluorescence microscopy, there are predominantly mesangial and some glomerular capillary wall granular staining with antisera specific for IgG 2+, IgA 1+, IgM 1+, C3 3+, C1Q 1+, kappa light chains 2+ and lambda light chains 1+. There is no extraglomerular staining. The electron microscopy reveals numerous mesangial and subendothelial immune complex-type electron-dense deposits. Rare subepithelial and intramembranous deposits are also identified. Endothelial tubuloreticular inclusions are present. There is effacement of the visceral epithelial cell foot processes with focal microvillous transformation. Pathology findings were consistent with class IV diffuse proliferative glomerulonephritis.

The patient was treated with a combination of corticosteroids and IV cyclophosphamide. Leuprolide acetate was used 2 weeks before the cyclophosphamide doses to suppress ovarian function. The hematuria and proteinuria improved by 2.5 months with a urine protein/creatinine ratio of 2.0, 5–10 RBCs/hpf on urinary microscopy, and serum creatinine decreased to 1.5 mg/dl. ACE inhibitor therapy was added. By 6 months, the urine protein/creatinine ratio was 0.5, urinalysis showed 2–5 RBCs/hpf of urine, and serum creatinine was 0.8 mg/dl. Based on this response, maintenance therapy was initiated with mycophenolate mofetil and ACE inhibition. The cyclophosphamide and leuprolide acetate were discontinued.

Anti-glomerular basement membrane disease

Anti-glomerular basement membrane (anti-GBM) disease is a rare immunologically mediated disease in which circulating antibodies target type IV collagen in the glomerular basement membrane. The resulting glomerulonephritis is acute, often rapidly progressive, and is associated with crescent formation. The anti-GBM autoantibodies react with the alveolar basement membranes, resulting in pulmonary disease. This combination of kidney and lung disease is known as Goodpasture syndrome. Patients presenting with pulmonary disease are believed to have a pre-existing pulmonary injury that exposes the alveolar basement membrane to the circulating autoantibody.[65–67]

Epidemiology

Anti-GBM disease may occur at any age, although two peaks – one in the third decade, mostly involving males, and a second in the seventh decade, with an equal gender distribution – are recognized. Most reports of anti-GBM disease are in Caucasian populations. This rare but severe disease is less common in Asians, and clinical outcomes in the latter population may differ, with fewer relapses, worse renal outcomes, and higher mortality rates than in Caucasian patients.[68]

Pathogenesis

Anti-glomerular basement membrane disease is an autoimmune disorder. Circulating pathogenic autoantibodies are directed against proteins in the non-collagenous globular domain (NC1 domain; exons 48–52) at the C-terminus of the alpha-3 chain of type IV collagen (COL4A3). The autoantibodies are IgG subclass, antigen driven, and T-cell dependent. The COL4A3 has limited distribution within the human body, which helps explain the unique tropism of anti-GBM disease. Patients with anti-GBM disease have normal alleles encoding the NC1 domain.[69] The two dominant epitopes for the anti-GBM antibodies reside on the COL4A3, and there is a strong association of Goodpasture syndrome with MHC class II, HLA-D allele (HLA DRB1-15 and HLA DQB1-6).[70]

The classic pathology of the renal biopsy in anti-GBM disease is a crescentic necrotizing glomerulonephritis. The pathology correlates well with the clinical diagnosis of a rapidly progressive glomerulonephritis. Immunofluorescence microscopy is intensely positive with linear GBM staining with antisera specific for IgG, C3, kappa light chains and lambda light chains. The linear immunofluorescence is in strong contrast to non-reactive basement membranes in Bowman capsule and tubular basement membranes. Other immuno globulin and complement components are typically absent. Immune complexes are not present by electron microscopy. Electron-dense fibrin tactoids, seen as fibrinogen reactive on

immunofluorescence microscopy, and fibrinoid necrosis by light microscopy, are present.

Clinical manifestations

The clinical features of a patient with anti-GBM disease include that of glomerulonephritis with active urine sediment, including dysmorphic RBCs, cellular casts, and significant proteinuria. Patients often develop oliguria and require dialysis. For those with alveolar basement membrane involvement, additional signs and symptoms of anti-GBM disease may include fever, cough, anemia, hemoptysis, pulmonary infiltrates, and frank pulmonary hemorrhage.[71] The upper airways and skin are typically not involved. The presence of pulmonary hemorrhage can be life-threatening. Prompt diagnosis and therapy are essential to improve the opportunity for kidney and patient survival.

Evaluation

The diagnosis of renal anti-GBM disease relies on serologic confirmation of a high titer of anti-GBM autoantibodies, and kidney biopsy showing linear immunofluorescence staining of IgG in the basement membranes. The differential diagnosis for a child presenting with a pulmonary–renal syndrome includes SLE, the ANCA vasculitides, and other non-specific pulmonary–renal syndromes.[72] Overlap syndromes do occur, with concurrent findings of anti-GBM antibodies and ANCA antibodies, for example. In this setting, it appears that the relapse risk is low, similar to that observed in anti-GBM disease.[73]

Treatment strategies

Management of anti-GBM nephritis includes the use of plasmapheresis, corticosteroids, and cyclophosphamide. Plasmapheresis is used to remove circulating anti-GBM antibodies and other mediators of inflammation. Corticosteroids add an additional anti-inflammatory effect. Cyclophosphamide is included in the therapeutic regimen in order to minimize new antibody formation. Plasmapheresis is instituted at diagnosis in those with pulmonary hemorrhage and for those with significant renal impairment. There have been no randomized controlled studies either in the adult or pediatric literature to determine the adequacy of this therapy or the overall outcomes in children.

Outcome

In observational studies, kidney and patient survival are linked to the severity of kidney disease and the presence or absence of pulmonary disease at presentation. Three risk levels were recently defined in an adult cohort. Diagnosis with a serum creatinine <5.7 mg/dl (approximate GFR >15 ml/min) was associated with a kidney survival of 95% and patient survival of 100% at 1 year. Presentation with a serum creatinine >5.7 mg/dl but not requiring dialysis predicted a 1-year kidney survival of 82% and patient survival of 83%. When dialysis was required at presentation, only 8% achieved recovery of renal function and patient survival was 65% at 1 year. Both kidney and patient survival declined in follow-up of these patients.[74] As anti-GBM disease is not considered a relapsing disorder, the marked decline in kidney and patient emphasize the necessity of early disease recognition and rapid institution of therapy.

Pauci-immune small-vessel vasculitis and glomerulonephritis

The term *pauci-immune* refers to the absence or minimal identification of an immunofluorescent (IF) staining pattern on renal biopsy. This lack of staining, or a very weak pattern, on IF distinguishes the pauci-immune glomerulonephritis from the immune complex-mediated vasculitides. The light-microscopic findings are typical of vasculitis: i.e. neutrophilic infiltration of the vascular wall, with varying degrees of fibrinoid necrosis in small vessels, including the glomeruli. This group of pauci-immune small-vessel vasculitides is pathologically indistinguishable, and therefore the clinical syndrome determines the unique diagnosis of Wegener's granulomatosis, Churg–Strauss syndrome, microscopic polyangiitis (MPA), or renal-limited pauci-immune vasculitis. The defining features of Wegener's granulomatosis and Churg–Strauss syndrome are biopsy-proven granulomatous disease, with eosinophilia in the latter (Table 16.3). MPA is a systemic non-granulomatous pauci-immune small-vessel vasculitis (SVV), whereas renal-limited pauci-immune vasculitis has signs and symptoms only of nephritis.

Epidemiology

Wegener's granulomatosis is a necrotizing granulomatous vasculitis that involves the kidneys and upper and lower respiratory tracts, as well as other organ systems. This disease is rare in children, with annual incidence reported as low as 1–2 per million, increasing to 1–2/100 000 in adults.[75] The incidence is greater in Caucasians compared with other races by nearly 9:1, and there is a slight male predominance. Churg–Strauss syndrome is extremely rare in childhood. In a review of the published literature, only 4 cases of Churg–Strauss syndrome have been reported; renal involvement was not noted in any of those patients.[72]

The epidemiology of MPA is more difficult to assess. In most reported series, MPA was not identified as a separate entity from polyarteritis nodosa, a vasculitis of medium-sized vessels.[76] This issue is further complicated by the fact that there is significant overlap between the clinical manifestations of Wegener's granulomatosis and MPA and it is possible that reported cases may have been inappropriately classified. From the Glomerular Disease Collaborative Network patient registry, of 38 children with small-vessel vasculitis, the diagnosis of MPA is 2.5 times greater than Wegener's granulomatosis, whereas that of renal-limited small-vessel vasculitis is 1.25 times less. No pediatric

Table 16.3 Features that allow differentiation of the small-vessel vasculitides

Feature	Henoch–Schönlein purpura	Microscopic polyangiitis	Wegener's granulomatosis	Churg–Strauss syndrome
Small-vessel vasculitis	+	+	+	+
PR3 positivity	0	+/–	+/–	+/–
MPO positivity	0	+/–	+/–	+/–
Necrotizing granulomas	0	0	+	+
Asthma and eosinophilia	0	0	0	+
IgA-dominant immune deposits on renal biopsy	+	0	0	0

+/– indicates this finding may be present.
PR3, proteinase 3; MPO, myeloperoxidase.

patient with Churg–Strauss syndrome was represented in this registry. These data suggest that Wegener's granulomatosis, as well as all of the small-vessel vasculitides, are rare in childhood.

Pathogenesis

Approximately 80% of the pauci-immune small-vessel vasculitides are associated with the serologic presence of antineutrophil cytoplasmic antibodies (ANCA).[77] Intracytoplasmic autoantigens, myeloperoxidase (MPO-ANCA; P-ANCA) and proteinase-3 (PR3-ANCA; C-ANCA) are the targets of these antibodies.

Debates about the pathogenicity of ANCA have been ongoing since the original descriptions of their association with small-vessel vasculitis. However, evidence based on animal models supports the possibility that ANCA is responsible for the induction of small-vessel vasculitis.[78] Investigation of ANCA-small-vessel vasculitis (ANCA-SVV) cohorts has identified factors such as exposure to silica as being possible inducers of ANCA formation. Such an exposure can result from farming, dusty trades exposure, and following an earthquake, as reported in Japan.[79]

Patients often report a flu-like illness at the onset of small-vessel vasculitis symptoms. However, no infectious causes have been linked to the onset of ANCA-SVV. It is possible that a patient with ANCA-SVV is predisposed to this disease by inheritance. Research designed to identify a specific genetic mutation linked to ANCA-SVV has not yielded a clear association. No reproducible association between Wegener's granulomatosis and a particular HLA has been identified,[80] although a recent finding in pooled DNA from a European cohort has suggested an association with HLA-DPB1.[81] Decreased efficiency of the alpha-1-antitrypsin gene product (the PiMZ and PiZZ phenotypes), which protects self against PR3, has been suggested. This association was made in a diseased cohort, but conversely the presence of the PiZ in a random population does not correlate with an increased incidence of PR3 disease in carriers.[82,83]

Finally, the genotypically determined level of expression of PR3 itself on the neutrophil membrane may be associated with Wegener's granulomatosis.[84] A novel theory of autoantigen complementarity[85] proposes that an inciting antigen elicits a cascade of immunologic events where a protein homologous to an antisense RNA from a non-coding strand of autoantigen initiates production of an antibody. An anti-idiotypic antibody may be produced to this complementary protein-generated antibody and this later event results in enough homology that an autoantigen is produced, resulting in susceptibility to self-antibody attack. Up to 50% of individuals transcribed complementary protein's antisense RNA. Additionally, some fungal and microbial organisms can trigger autoantigen complementarity. In summary, the ANCA-associated vasculitides are systemic diseases, where the interplay of autoimmunity with environmental and genetic factors determines their clinical expression.

The renal biopsy in patients with ANCA-mediated glomerulonephritis have crescents in 90% of cases, and over one-half of the renal biopsies will have >50% crescents in the sampled glomeruli.[77] The frequent crescent formation seen in ANCA-SVV is in contrast to immune complex-mediated glomerulonephritis (e.g. acute poststreptococcal glomerulonephritis, Henoch–Schönlein purpura), which have a lower frequency of crescent formation and, when crescents are present, rarely affect more than 50% of glomeruli. Segmental glomerular necrosis, characterized by karyorrhectic nuclear debris with fuchsinophilic 'fibrinoid' necrosis on trichrome stain, is frequent. GBM breaks, as well as disruption of Bowman capsule by the crescents, may be seen with periodic acid–Schiff (PAS) stains. The breaks in the GBM allow blood to escape the intravascular compartment, leading to the characteristic hematuria and urine sediment with dysmorphic RBCs seen. Renal biopsy IF microscopy is negative or reveals only weak ('pauci-immune') staining for immunoglobulins, usually IgM or complement component C3. Electron microscopy is notable for the absence of immune deposits, fibrin tactoids in areas of

necrosis, breaks in the GBM, and extraglomerular hypercellularity (crescents).

Clinical manifestations

The clinical presentation of Wegener's granulomatosis may include ear (otitis), nose (sinusitis, epistaxis, nasal ulceration), subglottic stenosis (hoarseness), and lung (pulmonary infiltrates and granulomatous lesions) involvement and glomerulonephritis. Constitutional symptoms are common and include weight loss and fever. Abdominal pain is a frequent finding. The Churg–Strauss syndrome is characterized by the history or presence of symptoms of bronchospasm, eosinophilia, and pulmonary infiltrates, along with systemic manifestations of vasculitis.

The clinical presentation for MPA is very similar to the other small-vessel vasculitides (Table 16.4). It is distinguished from Wegener's granulomatosis by the absence of granulomatous lesions and from renal-limited disease by the presence of at least one extrarenal organ system. Fever, weight loss, vasculitic rash, arthralgias, and pulmonary infiltrates are common. Pulmonary hemorrhage may be a severe, life-threatening manifestation of MPA. Ear and sinus involvement, although less common than in Wegener's granulomatosis, may be part of the constellation of symptoms. Renal-limited small-vessel vasculitis is pathologically identical to other pauci-immune glomerulonephritis but lacks concurrent vasculitis beyond the kidney. Although less frequent, the clinical presentation of pauci-immune glomerulonephritis may be subtle at times, with microhematuria and subnephrotic-range proteinuria as the only initial manifestations. However, active nephritis may present with oliguria, edema, and symptomatic renal failure.

Evaluation

As with lupus nephritis, the CBC, urinalysis, and a serum laboratory assessment of renal function and electrolytes are necessary to characterize the extent of the patient's disease. Anemia and leukocytosis are common. Inflammatory markers such as the ESR and CRP are elevated, often in parallel with disease activity.

ANCA testing is diagnostically useful for classifying patients into a broad diagnosis of ANCA-associated, pauci-immune small-vessel vasculitis. Laboratory testing for ANCA should include both an indirect immunofluorescence microscopy assay (IFA) and an enzyme-linked immunoassay (EIA). The IFA, using normal, alcohol-fixed, human neutrophils as substrate, produces two major staining patterns: the cytoplasmic pattern (C-ANCA) is represented by a diffuse immunofluorescence pattern of staining throughout the cytoplasm; the perinuclear pattern (P-ANCA), on the other hand, is represented by immunofluorescent staining that is localized to the cytoplasm surrounding the nuclei, leaving the rest of the cytoplasm relatively stain-free. Most C-ANCA are specific for proteinase 3 (PR3) and most P-ANCA are specific for myeloperoxidase (MPO), but this association is not absolute. For adequate diagnostic accuracy, an enzyme immunoassay should be used to specifically define the antigen that is being recognized by the IFA staining (i.e. PR3 or MPO). An abnormal result on EIA allows categorization of the patient into a specific antigen category. The presence of PR3 has been of some prognostic value, with an increased relapse risk associated with PR3 antibodies compared with MPO antibodies.[86]

ANCA tests have relatively good sensitivity for pauci-immune vasculitis, as nearly 90% of patients with this disease have a positive test. Serologic testing alone cannot be relied upon for diagnosis, since ANCA may be found in other disorders, such as SLE, inflammatory bowel disease, and with the use of several drugs. Categorization of the specific antigen involved has only limited usefulness for separating patients into the Wegener's granulomatosus versus MPA. Among Wegener's granulomotosis patients, 87% are PR3-positive, 11% are MPO-positive, and 2% are ANCA-negative.[87] Consequently, as the serologies are not definitive for placing the patient into a specific ANCA vasculitis disease category, clinical criteria must be

Table 16.4 Frequency of organ system involvement in children and adolescents with ANCA-associated small-vessel vasculitis

Organ system symptoms	All (N=38)	Microscopic polyangiitis (N=25)	Wegener's granulomatosis (N=10)	Renal-limited disease (N=3)
General	33 (87%)	22 (88%)	9 (90%)	2 (66.7%)
Dermatologic	12 (32%)	9 (36%)	3 (30%)	0
Ophthalmologic	2 (5%)	2 (8%)	0	0
Gastrointestinal	21 (55%)	17 (68%)	4 (40%)	0
Upper respiratory	24 (63%)	16 (64%)	8 (80%)	0
Lower respiratory	21 (55%)	13 (52%)	8 (80%)	0
Musculoskeletal	21 (55%)	15 (60%)	6 (60%)	0
Neurologic	3 (8%)	2 (8%)	1 (10%)	0
Renal	38 (100%)	25 (100%)	10 (100%)	3 (100%)

From the Glomerular Disease Collaborative Network Registry, 2004.

used for identification of the specific disorder. Ophthalmologic evaluation may document an episcleritis, scleritis, or optic neuritis. Nasal examination may reveal nasal ulceration with or without septal compromise. Chest radiograph or computed tomography (CT) may document an infiltrate. Renal ultrasound findings range from normal to increased echogenicity. Sinus imaging may reveal evidence of sinusitis in Wegener's granulomatosis, Churg–Strauss syndrome, and MPA. Bony erosion noted on sinus imaging is typical of Wegener's granulomatosis, and can account for a saddle nose deformity on physical examination in advanced disease. Biopsy of cutaneous lesions may reveal leukocytoclastic vasculitis, and lung biopsy may reveal capillaritis. Biopsy of the kidney in the presence of renal vasculitis will show pauci-immune necrotizing and crescentic glomerulonephritis. An older or chronic lesion may have additional fibrous crescents, glomerular sclerosis, and varying degrees of interstitial fibrosis.

Treatment strategies

The treatment of each of the pauci-immune vasculitides is similar, and is often guided by the degree of renal involvement, as well as the presence or absence of pulmonary hemorrhage. If renal impairment is present, and the biopsy contains evidence of active disease, immunosuppression is warranted. Cyclophosphamide and corticosteroids comprise the usual therapeutic regimen. In general, the treatment course is broken down into an induction phase, followed by a maintenance regimen. When a disease relapse occurs, relapse therapy mirrors the initial induction therapy.

Induction steroid therapy includes pulse intravenous methylprednisolone for three consecutive days. After this 3-day course, oral corticosteroids are initiated. Either IV or oral cyclophosphamide is added to the methylprednisolone. IV cyclophosphamide is usually given in monthly doses, starting at 500 mg/m^2, or oral dosing at 2 mg/kg/day, with a maximum oral dose of 150 mg/day. The WBC count nadir usually occurs between days 10–14 following IV dosing and is used to determine the need for dose adjustment. If the WBC count is less than 3000/mm^3, the next cyclophosphamide dose is held until recovery of the WBC count to above this level. The duration of induction therapy using IV cyclophosphamide is typically 6–12 months, dependent on response. A typical regimen may include monthly doses of IV cyclophosphamide followed by a maintenance regimen once remission has been established. When oral cyclophosphamide is used instead of IV cyclophosphamide, the WBC must be monitored intermittently, and if the WBC drops to below 3000/mm^3, the oral dose must be reduced, or even discontinued. In oral therapy, the duration of daily therapy is typically 3 months. This oral dosing scheme, although shorter than the IV regimen, is associated with a greater toxicity profile.

The transition to a maintenance phase of therapy is made once the patient has been declared to be in remission. Remission is generally believed to be present when the urine sediment is without hematuria or RBC casts. Normalization of the CRP or ESR may also be suggestive of remission; however, this is a less-specific measure. Residual proteinuria in the absence of other markers of disease activity may indicate chronic sclerotic glomerular lesions. Care must be taken when using the ANCA titer to determine the state of remission. It has been well documented that the ANCA titer does not always parallel disease activity.[86]

The addition of plasmapheresis for control of pulmonary hemorrhage has long been used for treatment of small-vessel vasculitis, and has been linked to improved patient survival. Recombinant factor VIIa therapy may also improve the likelihood of control of pulmonary hemorrhage and, therefore, improve patient survival.[88,89] An additional indication for plasmapheresis is severe kidney disease. Recent data from European studies suggest an improved renal survival with the addition of plasmapheresis in patients with small-vessel glomerulonephritis.[90] Addition of rituximab in induction therapy has been reported from some centers, but support for the efficacy and safety of this approach is not yet available.

The choice of a maintenance drug is somewhat more variable and may include azathioprine, mycophenolate mofetil, or methotrexate for non-renal manifestations. The optimal duration of maintenance therapy is not established. Varying regimens range between 6 months and a 3–4-year immunosuppression course. The use of trimethoprim-sulfamethoxazole in the induction phase of therapy has been proposed to reduce the risk of *Pneumocystis carinii* pneumonia.

Outcome

In cohort studies of children with ANCA glomerulonephritis, approximately 80–90% achieve a disease remission.[91,92] Of those achieving a remission, 40% subsequently relapse. Complications from ANCA small-vessel vasculitis may include chronic injury from severe multiorgan vasculitis and from therapeutic intervention. Mortality rates are approximately 3–10%. The majority of the mortality is in the acute setting, either due to the overwhelming vasculitis resulting in pulmonary hemorrhage, or infectious complications. Organ-specific morbidity may include chronic renal insufficiency, proteinuria, and hypertension from glomerulonephritis. Patients presenting with advanced stages of crescentic glomerulonephritis with a significant proportion of fibrous or fibrocellular crescents, interstitial and glomerular fibrosis are more likely to develop chronic renal failure despite control of active vasculitis. Of all patients presenting with ANCA glomerulonephritis, approximately 15–30% develop end-stage kidney disease less than 4 years from diagnosis.[91,92] Chronic lung disease may follow pulmonary capillaritis or pulmonary hemorrhage. Intestinal adhesions may follow intestinal vasculitis, and bowel ischemia may be observed. Subglottic stenosis can result in tracheal or bronchial stenosis. Nasal lesions can result in septal ulcerations and nasal deformities.

Morbidities from immunosuppression therapy include infection, alopecia, and hemorrhagic cystitis in the acute setting, and secondary malignancy in the long term. Malignancy, such as bladder cancer and myelodysplastic syndromes from

cyclophosphamide exposure, and skin cancer associated with azathioprine therapy, has been reported in adults with ANCA disease after immunosuppression therapy.[87,93] Secondary malignancies have, however, not been reported in pediatric ANCA cohorts.

Clinical case 2

A 12-year-old Caucasian female presented with a 4-month history of right-sided chest pain and cough. She had blood-tinged sputum two times during this period. Two attempts to treat a presumed pulmonary infection with antibiotics had failed. One month after her last course of antibiotics, the patient presented to the emergency room with severe abdominal pain and vomiting. She was found to have an elevated serum creatinine, as well as proteinuria and hematuria in urinalysis. She was admitted with the presumed diagnosis of postinfectious glomerulonephritis.

Past medical history and family history were non-contributory. The patient had noted a 10 lb (4.5 kg) weight loss over the preceding 10 months. No febrile episodes were reported. Further review of symptoms was negative for gross hematuria, edema, or joint disease. The patient reported a non-blanching rash on her thighs 3 months prior to admission.

On admission, her blood pressure was 137/89 mmHg and her temperature was 37.2°C. Her conjunctivae were clear, tympanic membranes were normal, and oropharynx was mildly erythematous. Nasal mucosa was pink and without lesion. There was no pretibial or pedal edema. Lung examination revealed rales over the right hemithorax and tachypnea. Hypoxemia was documented. The remainder of the physical examination was normal.

Chest X-ray revealed a right middle and upper lobe infiltrate. Urinalysis showed a specific gravity of 1.015, protein 1+, blood 2+, 1 RBC cast, 6–10 RBCs/hpf, no WBCs, and an occasional epithelial cell. The ASO antibodies, DNAse antibodies, and throat culture were negative. Complement, ANA, anti-dsDNA and hepatitis serologies were normal. CRP was 5 (normal 0–1.0 mg/dl), Hg was 10.5 g/dl, and WBC was 7600/mm^3. BUN was 37 mg/dl and creatinine 2.0 mg/dl. The patient's indirect immunofluorescence screen showed a cytoplasmic pattern and the PR3 EIA was 87.9 U/ml (normal < 20).

A renal biopsy was performed (Figure 16.8), which revealed greater than 95% cellular crescents. There was prominent glomerular fibrinoid necrosis (Figure 16.9). Interstitial scarring

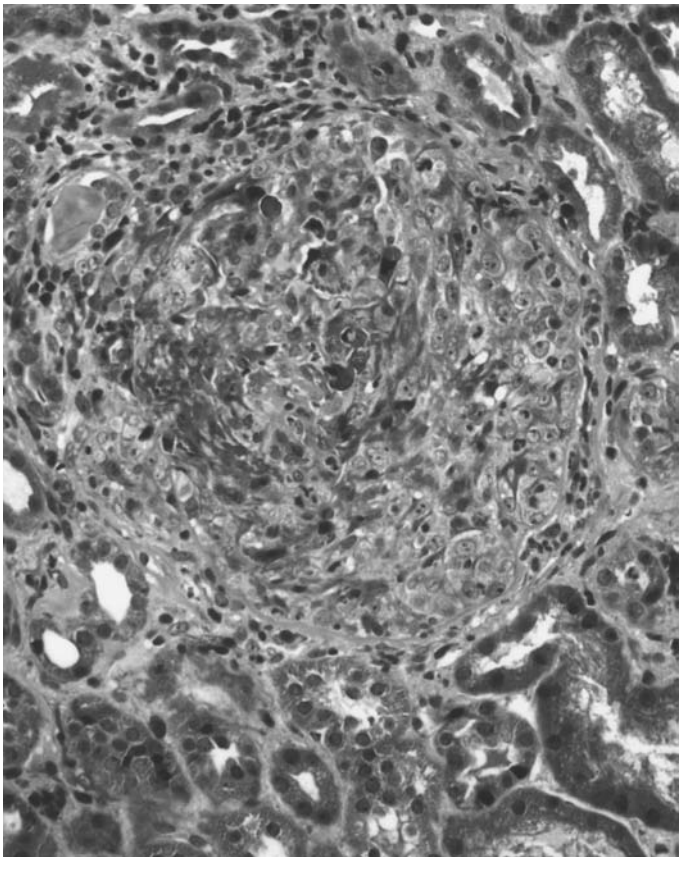

Figure 16.8 Clinical case 2. There is near total replacement of the usual glomerular histology by a large cellular crescent, 12-9 o'clock position. Fibrinoid necrosis is present at the 9 o'clock position and compressed residual glomerular capillary tuft is seen in the 10–11 o'clock location.

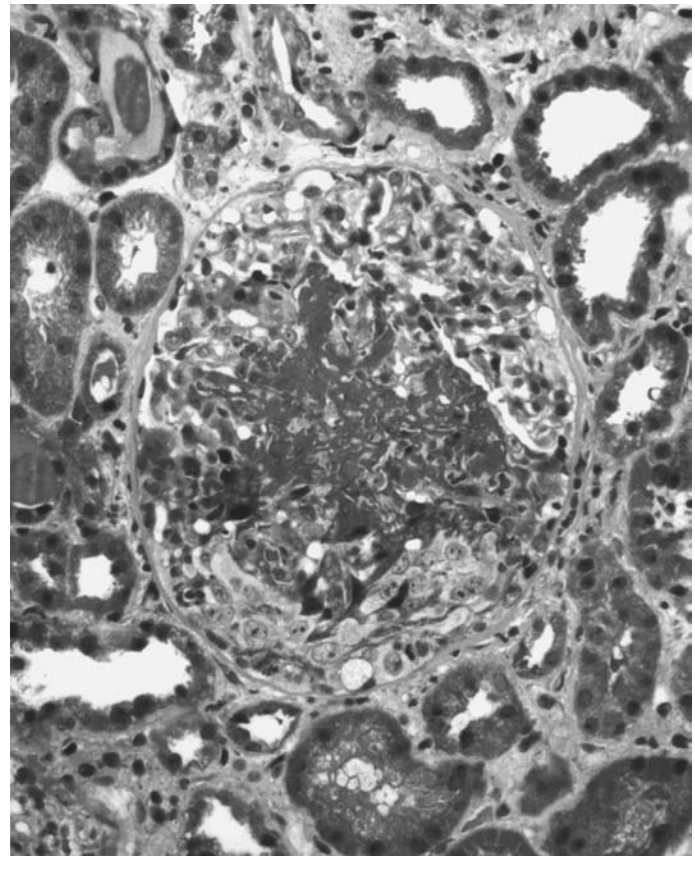

Figure 16.9 Clinical case 2. The center of the glomerulus is a stellate explosion of fibrinoid necrosis. A cellular crescent is present at the bottom half of the glomerulus and compressed normal glomerular capillary tuft is present on the superior half.

and tubular atrophy were present. Immunofluorescence was negative for immunoglobulins. A diagnosis of severe pauci-immune crescentic glomerulonephritis was made, and the patient was started on an initial dosing of methylprednisolone for 3 days as well as 6 cycles of monthly IV cyclophosphamide treatments. Hemoptysis resolved by week 1. Her clinical picture improved by dose three of intravenous cyclophosphomide with creatinine of 1.1 mg/dl and normal urine sediment.

Other vasculitides

The medium- and large-vessel vasculitides create injury in vessels too large to be present in the kidney. Disease in the vessels supplying the kidney from the aorta to the renal artery may indeed diminish blood flow to the glomerulus, thereby inducing renal manifestations of impaired glomerular filtration with an elevated serum creatinine and hypertension. The literature contains reports of polyarteritis nodosa causing glomerulonephritis. When strictly applied, the presence of the small-vessel vasculitis in the kidney precludes the diagnosis of a medium- or large-vessel vasculitis.

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17 Cystic kidney diseases

Larry A Greenbaum and Ellis D Avner

Cyst formation is seen in a variety of kidney diseases (Table 17.1). Many of these diseases are inherited, and many are associated with extrarenal manifestations. They are generally relatively rare diseases, although a few are common enough to cause considerable pediatric morbidity and mortality. Autosomal dominant polycystic kidney disease (ADPKD) is actually one of the most common human genetic diseases, but its clinical manifestations are usually mild in pediatric patients.

Identification of genes and proteins that are defective in the inherited cystic diseases has led to the discovery that most of these proteins are expressed in multimeric complexes at discrete subcellular locations in renal epithelial cells.[1] This expression in cilia, and in association with intercellular junction proteins and the focal adhesion kinase suggests that there may be a common pathway for cyst formation, through the abnormal integration of signal transduction pathways.[1,2]

Table 17.1 Classification of cystic kidney diseases

Polycystic kidney disease
Autosomal recessive polycystic kidney disease
Autosomal dominant polycystic kidney disease

Cysts of the medulla
Juvenile nephronophthisis
Medullary cystic disease
Medullary sponge kidney

Glomerulocystic kidney disease
Sporadic glomerulocystic kidney disease
Familial hypoplastic glomerulocystic kidney disease
Autosomal dominant glomerulocystic kidney disease

Multicystic dysplastic kidney disease
Simple renal cysts
Multilocular cysts
Acquired cystic kidney disease

Autosomal recessive polycystic kidney disease

The incidence of autosomal recessive polycystic kidney disease (ARPKD) has been estimated to be from 1 in 6000 to 1 in 55 000.[3,4] Since ADPKD can present in infancy and ARPKD can present in young adults, the designation ARPKD is more precise than the term 'infantile polycystic kidney disease.'

Genetics

All cases of ARPKD, a recessive disorder, are due to a mutation in the polycystic kidney and hepatic disease 1 (*PKHD1*) gene, which encodes the protein fibrocystin (also called polyductin).[5] There is a correlation between the type of mutation and the clinical presentation. Infants with two truncating mutations typically die as neonates, whereas the clinical presentation varies in children with at least one missense mutation, which presumably leads to some functional protein expression.[6]

Pathology

The kidneys are enlarged bilaterally and have a spongy appearance because of the cystic ectasia of the collecting ducts.[7] Large cysts are unusual in infancy, although there is a gradual increase in cyst size over time.[8] The microscopic appearance is dominated by the dilated collecting ducts, which are perpendicular to the kidney surface.

These patients have the typical features of congenital biliary plate dysgenesis. There is proliferation and dilation of bile ducts and, over time, fibrosis of portal tracts develops. These features, in addition to the presence of small distal portal veins, provide a microscopic explanation for the characteristic development of portal hypertension.[9]

Clinical manifestations

There is significant variability in the clinical features of ARPKD (Table 17.2). The majority of patients present during the first year of life, with a significant percentage presenting during the first month of life.[8,10,11] The most severely affected neonates have Potter syndrome due to oligohydramnios. Along with abnormal facies and joint deformities, these children have respiratory compromise due to pulmonary hypoplasia. Volume overload from renal failure and poor diaphragm function

secondary to the enlarged kidneys can also impair respiratory function. Death due to respiratory failure can occur in the first few days of life.[10]

The kidneys in ARPKD are typically large at birth and may increase in size. Along with impairing respiratory function, the enlarged kidneys may impair feeding and patient mobility.

Chronic renal failure and, ultimately, end-stage renal disease (ESRD), is the usual outcome in ARPKD. Kidney failure may be present at birth,[8,11] although it more typically develops gradually, with most children who survive the neonatal period not progressing to ESRD until later in childhood or even as young adults.[12] Many patients show some improvement in renal function during the first year of life, followed by a period of stabilization and subsequent decline.

Hypertension is very common, probably due to increased activity of the renin–angiotensin axis. It can be severe, potentially causing significant morbidity and even mortality. Most patients require antihypertensive therapy. Growth failure may occur due to the effects of chronic renal failure and to poor oral intake from abdominal distention.

There is a reported increased incidence of urinary tract infections (UTIs),[11,13] often associated with vesicoureteral reflux and catheterization;[14] it is more common in girls.[13,15] However, this may be overestimated, since pyuria is often present in the absence of infection.[8] Proteinuria may be detected, often intermittently,[11] but it is not of sufficient magnitude to cause clinical symptoms. Although microscopic hematuria is common, gross hematuria is quite uncommon, but has been reported.[12]

Acidosis develops with significant renal failure, but may be present earlier due to impairment in tubular acid excretion.[12] Patients almost always have a decreased ability to concentrate their urine,[11,12] and thus are at risk for dehydration and nocturnal enuresis. There is an increased risk of hyponatremia, which is most common in infants.[10,13]

Complications of portal hypertension due to congenital hepatic fibrosis include liver enlargement, splenomegaly, and esophageal varices.[10–12,14,15] Dilated biliary ducts predispose children with ARPKD to develop cholangitis.[13] Hepatocyte damage does not occur and synthetic function remains normal,[16] although mild abnormalities in liver enzymes are occasionally detected.[11,15]

Radiologic features

An intravenous pyelogram (IVP) shows enlarged kidneys with a delayed nephrogram.[17] Radial streaks due to contrast in the dilated collecting ducts are usually present in infancy, but may not be visible in older children. Because of concerns regarding intravenous contrast, a renal ultrasound is now the usual initial diagnostic test. Ultrasound shows enlarged kidneys, with increased echogenicity and poor corticomedullary differentiation; a hypoechoic rim is often visible (Figure 17.1).[18] Older children have increased medullary echogenicity, which may resemble nephrocalcinosis.[12] Multiple small cysts may be visible by ultrasound,[12,19] but this is quite variable. Macrocysts are sometimes visible in older children.[19]

Ultrasound detects liver abnormalities in approximately 50% of patients at the time of diagnosis.[12,13] It is often possible to detect dilations of the peripheral intrahepatic biliary ducts and the principal bile duct. There may also be evidence of portal hypertension, particularly in older patients.[12]

Diagnosis

A large percentage of children are now diagnosed by an abnormal prenatal ultrasound.[13] The presence of bilaterally enlarged kidneys during the first few years of life is suggestive of ARPKD. The radiologic features, as detailed above, can be helpful, but

Table 17.2 Presenting manifestations in autosomal recessive polycystic kidney disease

Prenatal
Abnormal prenatal ultrasound
Postnatal
Respiratory distress
Enlarged kidneys
Renal failure
Hypertension
Pyuria
Proteinuria
Failure to thrive
Hepatomegaly
Esophageal varices
Family history
Renal cystic disease in a sibling

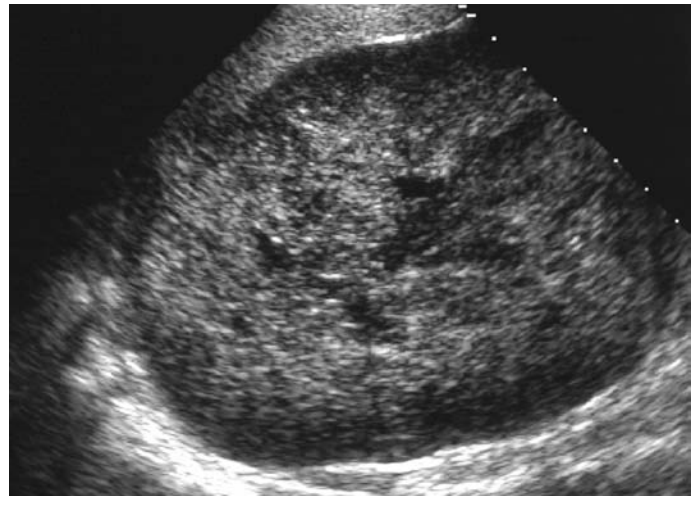

Figure 17.1 Sonogram of an infant with autosomal recessive polycystic kidney disease. The kidneys are enlarged and echogenic; renal cysts are not well visualized. Cortical rim is hypoechoic.

are not always conclusive. This is especially true in older patients with ARPKD, since cysts may become enlarged and thus ultrasound features may resemble those seen in ADPKD.[20] Consideration must be given to an early presentation of ADPKD, and therefore it is now common to augment the family history with renal ultrasounds of the parents to rule out this possibility. For inconclusive cases, histologic examination of the liver is useful, since congenital hepatic fibrosis is always present in ARPKD and is extremely rare in ADPKD. Liver ultrasound may also demonstrate hepatic disease.[12]

Genetic diagnosis, which is not yet commercially available, is challenging because the *PKHD1* gene is extremely large and complex, and the known mutations are quite heterogeneous.[6] Mutations are more likely to be detected in children with severe ARPKD than in children with moderate disease.[6] Linkage analysis improves the diagnostic yield if there is an affected sibling.[21]

Tuberous sclerosis, Meckel's syndrome, von Hippel–Lindau disease, nephroblastomatosis, and bilateral Wilms' tumor are part of the differential diagnosis of enlarged kidneys. Transient nephromegaly of the newborn can be confused with ARPKD,[22] but this resolves relatively quickly.

Treatment

The initial management of respiratory distress is quite challenging. Both unilateral and bilateral nephrectomies, by decreasing the effect of abdominal distention, have been successfully used to improve respiratory function and allow children to wean from respiratory support.[23] Yet, many neonates still die due to underlying pulmonary hypoplasia.

After hospital discharge, infants require frequent monitoring and adjustment of their treatment regimen, including diet, sodium and fluid intake, and antihypertensive therapy. The patient's status may be altered markedly by changes in oral intake, upper respiratory infections, or adjustments in medications. Patients usually become less medically fragile as they get older.

Hypertension mandates aggressive treatment. In unusual cases, it may be refractory to medical therapy and require bilateral nephrectomies and the initiation of peritoneal dialysis.[14] Chronic renal failure and ESRD are managed using the usual strategies.

Complications of portal hypertension need to be addressed. Esophageal varices may require sclerotherapy or placement of a portacaval shunt. Cholangitis needs to be aggressively treated with antibiotics. Splenectomy has been performed in children with intractable hypersplenism that causes anemia and thrombocytopenia.[14] Liver transplantation is occasionally necessary.[13]

Prognosis

Much of the mortality occurs in the first year of life, especially during the first month.[10–13] Respiratory failure and sepsis are currently the most common causes of death.[13] In a long-term follow-up study, children who survive beyond the first month have a 5-year survival of 87% and 15-year survival of 67%.[14]

Autosomal dominant polycystic kidney disease

ADPKD, with an incidence of 1:500 to 1:1000, is the most common inherited kidney disease. Although kidney involvement is the major feature for most patients, there are protean extrarenal manifestations, including the potentially life-threatening possibility of a ruptured intracranial aneurysm. Severity varies greatly between patients and symptoms tend to develop over time.

Genetics

ADPKD is a genetically heterogenous condition; disease occurs due to mutations in one of at least two separate genetic loci. Patients with a mutation of the *PKD1* gene,[24] which is located on chromosome 16, account for approximately 85% of cases. Most remaining cases are due to a mutation in the *PKD2* gene on chromosome 4.[25] Patients with *PKD2* gene mutation have less severe symptoms.[26] At a molecular level, the disease is 'recessive' in that a somatic mutation is required in addition to a germ-line mutation.[27] This may explain the clinical heterogeneity of the disease, even within families. There may be additional loci.

Pathology

The kidneys are enlarged and have multiple cysts, which can originate from any segment of the nephron. Except for cysts, the renal architecture is initially normal, although, as the disease progresses, glomerulosclerosis gradually increases and progressive fibrosis becomes a major feature.

Clinical manifestations

Most children with ADPKD are asymptomatic, and increasing numbers of these patients are diagnosed based on a positive family history followed by screening computed tomography (CT) scan or ultrasound. Others are diagnosed after kidney cysts are incidentally noted on an imaging study, including prenatal ultrasound.

There are reports of severe disease, including neonatally lethal disease, typically secondary to respiratory failure, associated with massively enlarged kidneys.[11,28] Most neonates diagnosed on the basis of an abnormal prenatal ultrasound are asymptomatic. The majority of these children maintain normal renal function, but some will reach ESRD during childhood.[12,28,29]

Most children with symptomatic ADPKD present in late childhood or adolescence.[11,12] Visible hematuria, which is rare in ARPKD, is quite common in adults with ADPKD and can manifest in childhood.[11,12,30] Other presenting symptoms include hypertension, urinary frequency, abdominal or flank pain, abdominal mass, UTI, and proteinuria (Table 17.3).[11,12,30,31]

Table 17.3 Presenting complaints in symptomatic children with autosomal dominant polycystic kidney disease

Presenting complaint	Number of patients
Neonatal disease[a]	10
Hematuria	7
Abdominal pain	5
Hypertension	4
Renal mass	2
Frequency	2
Urinary tract infection	2
Proteinuria	1

This table combines the results of 3 case series.[11,12,31]
[a]Neonatal disease includes patients who presented in the first month of life with enlarged kidneys, respiratory distress, or Potter's syndrome.

Table 17.4 Extrarenal manifestations of autosomal dominant polycystic kidney disease

Cardiovascular
Mitral valve prolapse
Aortic aneurysms
Hypertension
Intracranial aneurysms

Extrarenal cysts
Hepatic cysts:
Pancreatic cysts
Ovarian cysts
Testicular cysts:
Arachnoid cysts
Splenic cysts
Pineal cysts
Seminal vesicle cysts

Other
Hernias
Colonic diverticula
Cholangiocarcinoma
Congenital hepatic fibrosis

In one study, the mean age of death or onset of ESRD was 53 years in patients with a *PKD1* mutation and 69 years in patients with a *PKD2* mutation.[26] The majority of patients who are symptomatic during childhood do not develop renal insufficiency as young adults,[12] but they may be at a higher risk for early kidney failure.[30]

The presence of symptoms in children correlates with the number of cysts. Children with more than 10 cysts have an increased incidence of flank or back pain, palpable kidneys, and hypertension.[31] Such children also have more complaints of palpitations and urinary frequency than their unaffected siblings.[31]

Hypertension and resultant end-organ damage occur in children with ADPKD. Hypertension is more common in teenagers, who are also more likely to have an increase in left ventricular mass.[32]

Some children with mild ADPKD have a subtle defect in urinary concentrating ability,[12] and this is more common in children with more than cysts detected by renal ultrasound.[31] Children with 10 or more on ultrasound cysts have an increased incidence of proteinuria.[33] Kidney stones, often presenting as acute flank pain, are increased in adults,[34] but are infrequent in children.

Kidney infections are more common in patients with ADPKD, and complications may include perinephric abscess, septicemia, and death;[35] there may be an increased risk of vesicoureteral reflux.[36] Cyst infection is especially troublesome, since the urine culture may be negative, and not all antibiotics achieve therapeutic levels in the cyst fluid.[35]

There are a large number of possible extrarenal manifestations in adults with ADPKD (Table 17.4). Among a group of children, 12% had mitral valve prolapse (vs 3% of controls) and the incidence increased with age.[37] Inguinal hernias are substantially increased in children.[30,31] Liver cysts, the most common manifestation in adults, are rare in children.[31]

Ruptured intracranial aneurysms are a significant cause of mortality in adults with ADPKD.[38] In one study, the mean age at bleeding was 39.5 years but 10% of patients were less than 20 years.[39] There are reports of young children with ruptured intracranial aneurysms.[40] Aneurysms cluster in families,[41] and thus a positive family history for intracranial hemorrhage or aneurysm is an important risk factor, which mandates screening in such families.

Radiologic features

Ultrasound and CT scan are useful for detecting macroscopic cysts (Figure 17.2). The number and size of cysts in children increases with age, and those children with more cysts have increased kidney size.[31] Increased renal echogenicity may be seen in some children.[19] Occasionally, children can have marked disease asymmetry, which can create diagnostic confusion.[42]

Diagnosis

Rare, early-onset ADPKD can sometimes be diagnosed by prenatal ultrasound,[43,44] although most cases are identified in the last 10 weeks of gestation. The kidneys are large, with increased echogenicity, and cannot easily be distinguished from the kidneys of children with ARPKD. Occasionally, macrocysts are identified.[45] Early diagnosis in a fetus with an affected parent is possible using DNA analysis.[46]

Even after birth, it is often difficult to distinguish early-onset ADPKD from ARPKD. Radiologic studies of the kidneys are often inconclusive. Liver imaging or biopsy is useful, because biliary plate abnormalities are always present in ARPKD and extremely rare in ADPKD. The presence of a parent with ADPKD is the most useful diagnostic clue. Yet, many parents

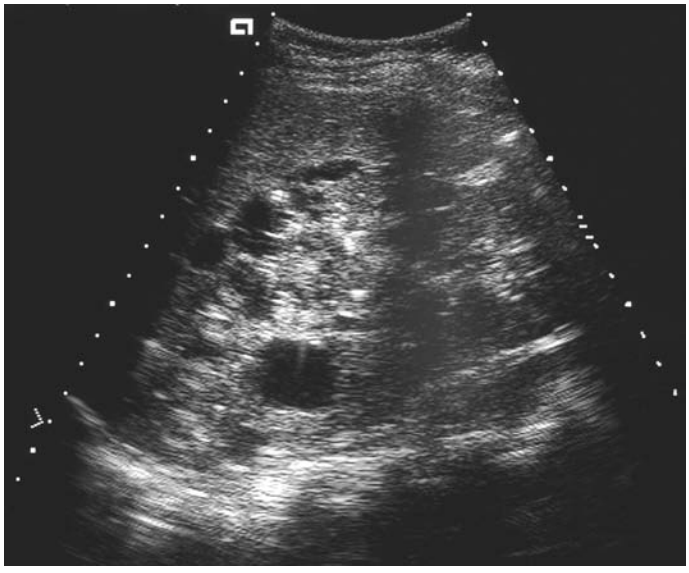

Figure 17.2 Sonogram of a 17-year-old patient with autosomal dominant polycystic kidney disease. Cysts of varying sizes are located in the cortex and the medulla.

Table 17.5 Sensitivity and specificity of ultrasound for detecting autosomal dominant polycystic kidney disease in children

Age	Specificity (%)	Sensitivity (%)
3 months to 5 years	89	62
5 years to 10 years	100	82
10 years to 15 years	100	86
15 years to 17.5 years	100	67

Adapted from Gabow et al.[47]
This table summarizes the results of ultrasound screening in a group of children with PKD1 by linkage analysis. The presence of a single cyst was interpreted as a positive ultrasound. Current ultrasound technology probably has an increased sensitivity.

are unaware of their own disease,[12] and thus screening imaging studies of 'normal' parents are mandatory.

Diagnosis in asymptomatic or mildly symptomatic children is usually accomplished by renal ultrasound. The sensitivity and specificity of this approach increase with the child's age (Table 17.5). Unilateral cysts may be the only initial finding in children with ADPKD,[12,31] and in the context of a positive family history even a single cyst is highly suggestive of disease.[47] For adults, given the increased incidence of benign solitary cysts, more stringent criteria are necessary to avoid false positives.[48]

The ability to screen patients for mutations in the *PKD1* and *PKD2* genes is commercially available, although false-negative results can occur.

Screening and monitoring

Many children have a parent with ADPKD, and therefore have a 50% risk of carrying the defective gene. Undiagnosed, asymptomatic patients may have significant abnormalities such as hypertension, proteinuria, bacteriuria, and an increased serum creatinine.[49] Certainly, at-risk children need periodic screening, with special attention to monitoring blood pressure. Screening ultrasounds are not recommended because of concerns regarding qualification for health insurance and creation of 'fragile child' syndrome. Figure 17.3 presents a basic approach to monitoring the child with a diagnosis of ADPKD, with the caveat that monitoring needs to be customized for the individual patient.

Treatment

Children with severe disease receive standard therapy for chronic renal insufficiency. A variety of interventions to slow the progression of ADPKD have been tested in animal models. At this stage, the most likely therapies to translate from such models are inhibition of the vasopressin V2 receptor and the expression of the epidermal growth factor axis.[50] A phase II clinical study of the former is underway in Japan for ADPKD and a phase I-II study of the latter is being planned for ARPKD in 2006.

Hypertension is fairly common in older children with ADPKD and should be treated. In adults with ADPKD, rigorous control of blood pressure was superior to standard control in reversing left ventricular hypertrophy.[51] An angiotensin II receptor blocker, when rigorously tested, was superior to a dihydropyridine calcium channel blocker in slowing the progression of chronic renal insufficiency in ADPKD at similar levels of blood pressure control.[52] Angiotensin-converting enzyme (ACE) inhibitors reverse left ventricular hypertrophy in hypertensive adults with ADPKD.[53]

UTIs should be treated promptly, with awareness for the increased risk of abscesses and septicemia. Cyst infection requires selection of an antibiotic that penetrates the cyst such as trimethoprim-sulfamethoxazole[54] or ciprofloxacin;[55] occasionally, cyst aspiration may be necessary.[56] Patients with intractable pain from renal cysts can benefit from either cyst aspiration, surgical reduction, or thoracoscopic denervation.[57]

The possibility of a ruptured intracranial aneurysm is a frightening, albeit rare complication in pediatric patients. The advisability of screening patients is currently being debated. Magnetic resonance angiography (MRA) is a safe and sensitive approach for detecting an asymptomatic aneurysm.[58] However, there is a need to balance the safety and efficacy of surgical intervention with the risk of aneurysm rupture. Because of the familial predilection to aneurysm formation,[58,59] screening of older teenagers with a positive family history is a reasonable approach.[60]

Nephronophthisis

Nephronophthisis (NPH), a recessively inherited disorder, is one of the most common causes of ESRD in children. It is often

grouped with dominantly inherited medullary cystic disease because of an overlapping radiologic and histologic appearance. However, medullary cystic disease is genetically distinct and usually presents in adulthood.

Genetics

Mutations at four different loci may cause NPH (Table 17.6), and additional genetic heterogeneity is likely.[61] The majority of cases of NPH are due to mutations in the *NPHP1* gene.[62] Most patients with nephronophthisis type 1 are homozygous for a large deletion that affects the *NPHP1* gene.

Pathology

On light microscopy, there is diffuse interstitial fibrosis with mononuclear cell infiltration. Along with tubular atrophy, there is extreme thickening and lamellation of the tubular basement membranes. Electron microscopy confirms this thickening, and also shows splitting of the basement membrane. Cysts appear to originate from the distal convoluted tubules and collecting ducts. The glomeruli may be normal or have periglomerular fibrosis with thickening of Bowman capsule; glomerular obsolescence eventually develops.[63]

Clinical manifestations

Polyuria and polydipsia due to poor urinary concentrating ability lead to dehydration, nocturia, and primary or secondary nocturnal enuresis.[63] Renal sodium wasting leads to salt craving in some children. The urinalysis is notable for the absence of abnormalities,[63] although low levels of tubular proteinuria are sometimes present. Glycosuria is also occasionally present. Hypertension is unusual, except in patients with NPH type 2.

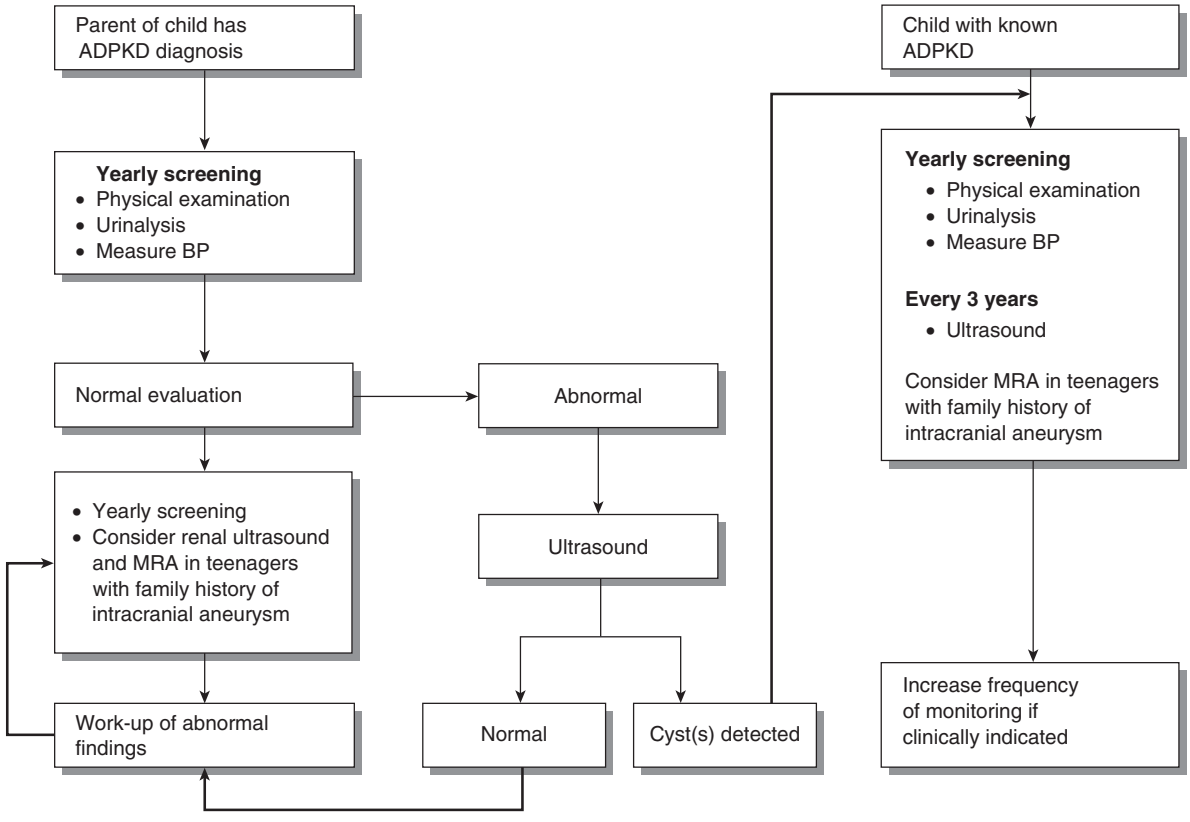

Figure 17.3 An algorithm for screening and monitoring of children with possible autosomal dominant polycystic kidney disease.

Table 17.6 Genetic heterogeneity of nephronophthisis

Type	Chromosome locations	Gene mutated	Encoded protein	Clinical form
NPH type 1	2q13	*NPHP1*	Nephrocystin	Juvenile
NPH type 2	9q22	*NPHP2*	Inversin	Infantile
NPH type 3	3q22	*NPHP3*	Nephrocystin-3	Adolescent
NPH type 4	1p36	*NPHP4*	Nephrocystin-4	Juvenile

Patients frequently have symptoms of chronic renal failure, such as fatigue, anorexia, and growth retardation.[64] Children with NPH have an anemia that is out of proportion to their degree of renal failure.[64] Patients with NPH type 1 develop ESRD at a mean age of about 10–13 years.[63,65]

NPH type 2 is distinct from the other forms of NPH. Renal failure occurs in infancy, and the kidneys are large with widespread cysts.[66] Hypertension is more common than in other forms of NPH. *NPHP2* gene defects may also lead to situs inversus in a minority of affected children.[66] The timing of ESRD is fairly similar in NPH type 1 and NPH type 4, whereas ESRD develops at a mean age of 19 years old in NPH type 3.[65,67]

Senior–Loken syndrome is the combination of NPH with tapetoretinal degeneration. In the early-onset form, called congenital amaurosis of Leber, nystagmus is usually present, there is an absent pupillary response to light, and most patients are blind or severely visually impaired.[68] There is a late-onset form of Senior–Loken syndrome in which visual impairment develops during childhood. Moreover, patients with a defect in the *NPHP1* gene may have ocular findings, including areas of retinal atrophy with flat or low-voltage electroretinograms. However, these patients are usually asymptomatic, and probably should not be considered to have Senior–Loken syndrome.[69] Senior–Loken syndrome has been described in children with mutations in the *NPHP3* and *NPHP4* genes, although most of these patients do not have Senior–Loken syndrome. Some children with NPH have other extrarenal manifestations, including mental retardation, ocular motor apraxia Cogan type, Joubert's syndrome, Dandy–Walker syndrome, cerebellar ataxia, coloboma, and skeletal anomalies.

Radiologic features

By ultrasound, the kidneys are hyperechoic with loss of corticomedullary differentiation; they are of normal or slightly decreased size. Medullary cysts are a hallmark of the disease, but they are not always detected by ultrasound. CT is a more sensitive method for identifying medullary cysts and thin-section CT is recommended.[64]

Diagnosis

The diagnosis of NPH can be challenging, especially in patients without extrarenal manifestations. Polyuria and polydipsia, salt craving, disproportionate anemia, a benign urinalysis, and the age of presentation are important clues. The detection of medullary cysts in the setting of chronic renal failure in a child with small, echogenic kidneys is virtually diagnostic. Renal biopsy may improve diagnosis, but is rarely indicated. Genetic diagnosis is now possible because screening for the large chromosomal deletion in the *NPHP1* gene is relatively easy, and this will identify approximately 60% of patients with NPH.[70] Moreover, sequencing of the entire *NPHP1* gene for mutations is commercially available for those patients with NPH type 1 who do not have the large deletions. All patients should have an ocular examination to screen for Senior–Loken syndrome and a liver ultrasound to screen for hepatic fibrosis. NPH is also discussed in Chapter 12.

Treatment

There is no specific therapy available for NPH. Families should be counseled regarding the risk of dehydration due to polyuria. The anemia responds to erythropoietin therapy. Children receive standard therapy for chronic renal insufficiency and ultimately require dialysis and transplantation.

Medullary cystic disease

Medullary cystic disease (MCD) is an autosomal dominant disorder. ESRD typically develops during adulthood, although renal insufficiency may be apparent during childhood.[71,72] Hyperuricemia with gouty arthritis may be the presenting manifestation.[71,73] Other clinical features include polyuria, anemia, and hypertension.[74,75] The kidneys are usually normal or small, and renal imaging may infrequently show a few medullary cysts.[71] The urinalysis is typically benign, except for low-grade proteinuria in a minority of patients.[74] Histologic examination demonstrates interstitial nephritis with prominent thickening and splitting of tubular basement membranes.[71,76]

Mutations in *UMOD*, the gene encoding uromodulin (also called Tamm–Horsfall protein), cause MCD type 2.[77] The dominant features are chronic renal failure and gout.[76] Genetic diagnosis, by sequencing of exons 3 and 4, the sites of most mutations in this disorder, is commercially available (see http://www.genetests.org). The locus for MCD type 1 has been identified on chromosome 1. These patients tend to have fewer manifestations of hyperuricemia than patients with MCD type 2 and usually have a later onset of renal insufficiency.[74] There is evidence for additional genetic heterogeneity.[74]

Multicystic dysplastic kidney

The incidence of multicystic dysplastic kidney (MCDK) is estimated at 1 in 2500 newborns;[78] it is one of the most common fetal anomalies detected by prenatal ultrasound. Most cases are unilateral and asymptomatic; rare bilateral disease is usually fatal at birth due to Potter's syndrome. The widespread use of prenatal ultrasound has led to more frequent diagnosis of MCDK, and the approach to the management of these patients is evolving.

MCDK is typically composed of cysts of varying size that do not appear to communicate with each other or the collecting system, and a small amount of abnormal-appearing renal parenchyma. The ureter from the affected kidney is atretic. On microscopic examination, the tissue between the cysts is dysplastic, with undifferentiated mesenchymal cells, often with cartilage, and immature glomeruli and tubules.

Most cases of MCDK are sporadic, although families with putative autosomal dominant inheritance have been described.[79] The pathogenesis of MCDK has been attributed to either early ureteral obstruction[80] or disruption of the normal mechanism of induction of the metanephric blastema by the ureteric bud.[81]

Currently, most MCDKs are diagnosed by prenatal ultrasound. A unilateral palpable abdominal mass, typically in the neonate, is also a common presentation.[82] In older children, MCDK is occasionally diagnosed during the evaluation for abdominal pain or mass, hematuria, or hypertension. At any age, MCDK may be discovered during abdominal imaging for evaluation of UTI or other unrelated symptoms.

In infants with a prenatal diagnosis, a postnatal ultrasound should be performed to confirm the presence of MCDK. It may be difficult to differentiate MCDK from severe hydronephrosis.[83] In MCDK, there is typically no communication between cysts, and the larger cysts are not medial (Figure 17.4). In hydronephrosis, the calyces extend outward from the dilated renal pelvis, and there is functional renal parenchyma surrounding the central cystic structure. If the diagnosis is unclear, a radionuclide scan shows uptake of tracer if hydronephrosis is present, but usually no uptake with MCDK.

Children with MCDK are likely to have abnormalities of the contralateral kidney. Vesicoureteral reflux (VUR) has been reported in 4–31% of contralateral kidneys. Other reported anomalies include ureteropelvic junction (UPJ) obstruction, ureteral ectopia, uterovesical junction obstruction, ureterocele, and renal dysplasia.[84]

The natural history of MCDK is usually gradual involution. In one study, 18% were undetectable by ultrasound at 1 year of age, and 58% were undetectable by 6 years of age.[82]

Hypertension, which is postulated to be renin-mediated, has been reported as a potential complication of MCDK. There are reports of hypertension being cured following surgical removal of the MCDK.[85] Yet, others have questioned the validity of these reports. For example, in a series of 260 cases of MCDK, there were only 4 patients with hypertension of uncertain etiology and significance.[86]

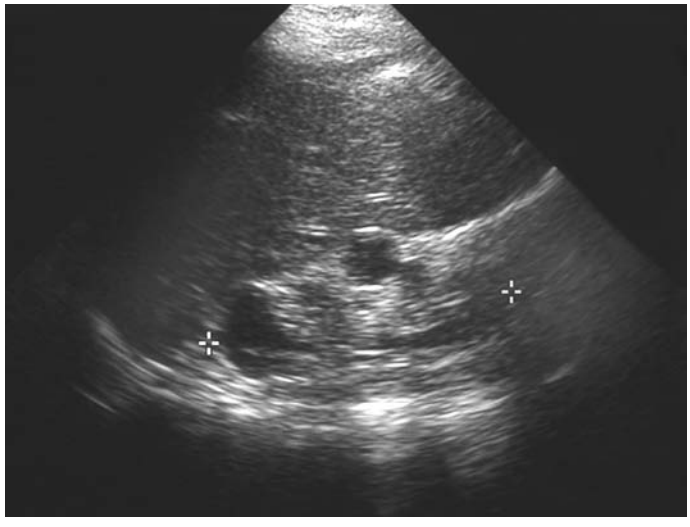

Figure 17.4 Sonogram of a 14-month-old child with a multicystic dysplastic kidney. The parenchyma is echogenic and the cysts are peripheral.

Malignancy is another reported complication of MCDK. Wilms' tumor in younger children[87] and renal cell carcinoma in older teenagers and adults have been reported in association with MCDK.[88] The actual risk is unclear. Fewer than 0.1% of the 7500 children enrolled in the National Wilms Tumor Study Group had a MCDK.[89]

The management of MCDK is controversial. Initially, concern regarding the neoplastic potential of dysplastic tissue led to routine surgical removal. However, many clinicians now employ regular surveillance by sonography and clinical evaluation.[86] There is no consensus on the recommended frequency of ultrasound evaluations, particularly given the low risk of Wilms' tumor. Ultrasounds are usually performed every 3 months during the first year of life, and then every 6–12 months until approximately 5 years of age.[82] Surgical removal, which may be done laparoscopically, is indicated if there is any enlargement or change suggesting malignant transformation. Other indications for nephrectomy include mass effect, pain, hypertension, and parental preference.

Follow-up, and surgical repair when indicated,[84] of the contralateral kidney is also critical. The follow-up ultrasounds of the MCDK should evaluate the size and echogenicity of the contralateral kidney; there should be compensatory hypertrophy.[90] Given the high rate of VUR, a routine voiding cystourethrogram is frequently recommended,[91] although this has been questioned in the child with a normal-appearing contralateral kidney.[84] MCDK is also discussed in Chapter 1.

Medullary sponge kidney

Medullary sponge kidney (MSK) is predominantly a disease of adults, but occasionally presents in childhood. Pathology consists of asymmetric, focal dilation of intrapapillary collecting ducts with multiple small cysts. Although family clusters have been reported, MSK does not have a defined genetic basis.

The diagnosis of MSK is based on characteristic IVP changes: stagnation of contrast in one or more renal papillae due to dilation of the collecting ducts. The resultant image has been described as a 'pyramidal blush'.

Clinically, patients often present with nephrolithiasis and/or UTI. There may be impairment of urinary concentrating ability or urinary acidification (renal tubular acidosis; RTA), but the glomerular filtration rate is normal. The urinary concentrating defect can lead to complaints of polyuria in a child.[92] Hematuria and hypercalciuria are common, even in the absence of symptomatic nephrolithiasis.

Treatment is symptomatic. Nephrolithiasis is successfully treated by standard modalities, including extracorporeal shockwave lithotripsy. Patients with MSK and RTA have a good response to alkali therapy, with decreased hypercalciuria and stone formation.[93]

Glomerulocystic kidney disease

Glomerular cysts are present in a variety of diseases (Table 17.7); the diagnosis is made by kidney biopsy. The term 'glomerulocystic kidney disease' is reserved for patients who do not have an underlying syndrome or disease such as ADPKD. As detailed below, glomerulocystic kidney disease (GCKD) is not a uniform, well-defined entity; rather, it describes a heterogenous group of patients who have been grouped into categories based on apparent inheritance and kidney size.

Children with non-syndromal, sporadic GCKD have a variable presentation, and can be indistinguishable from infants and children with ADPKD. The kidneys are frequently enlarged at birth, with a loss of corticomedullary differentiation. Ultrasound and magnetic resonance imaging (MRI) can identify cortical cysts.[18] Renal function may be normal or decreased.[94]

There is an autosomal dominant form of GCKD that is associated with small (hypoplastic) kidneys and malformed or absent calyces.[95] Glomerular filtration rate (GFR) in these children is decreased at birth, but then renal function remains fairly stable. In some families, hypoplastic GCKD is secondary to mutations in hepatocyte nuclear factor (HNF)-1β, which may also cause maturity-onset diabetes of the young (MODY), and thus affected patients may have renal disease and diabetes.[96]

The remaining families with GCKD have normal or increased kidney size. These patients have hypertension, and renal function ranges from normal to ESRD. The kidneys are large and echogenic; pelvocaliectasis and a hypoechoic cortical rim are additional sonographic features. Inheritance is autosomal dominant.

Simple renal cysts

The increased use of radiologic testing has led to the identification of more children with simple cysts, which may be solitary or multiple. The incidence of simple cysts increases with age.

Table 17.7 Disorders associated with glomerular cysts

Syndromes with glomerular cysts
Brachymesomelia–renal syndrome
Oral–facial–digital syndrome
Glutaric acidemia type II
Trisomy 18
Renal retinal dysplasia:
Short-rib polydactyly syndrome type II
Tuberous sclerosis
Zellweger syndrome
Autosomal dominant polycystic kidney disease
Sporadic glomerulocystic kidney disease
Familial hypoplastic glomerulocystic kidney disease
Autosomal dominant glomerulocystic kidney disease

Less than 0.3% of children have simple renal cysts, and they are usually not associated with subsequent problems.[97] Cysts in children usually do not increase in size, and single cysts are commonly located in the right upper pole.[97] However, the presence of even a single cyst in the context of an appropriate family history supports a diagnosis of ADPKD.[47] Cysts in children occasionally cause pain. Most children with simple renal cysts only need routine ultrasound follow-up, unless the cysts are atypical and therefore suggestive of a malignancy.

Multilocular cysts

A multilocular cyst is a unilateral, benign tumor of the kidney. Approximately half the cases occur in children, with the remainder in middle-aged adults. Children are usually less than 2 years of age, and the most common presenting complaint is an abdominal mass. Pathologically, the multilocular cyst is well encapsulated and non-infiltrating. The multiple cysts, which do not communicate, are typically separated by fibrous tissue, although embryonic tissue is sometimes present, especially in pediatric cases. The differential diagnosis includes Wilms' tumor, ADPKD, or a multicystic dysplastic kidney. Because of the possibility of a cystic Wilms' tumor, surgical resection is recommended. Nephrectomy is sometimes the only option, but increasing numbers of cases are managed with partial nephrectomy to preserve functional parenchyma.[98]

Acquired cystic kidney disease

Kidney failure is sometimes associated with cyst formation in a previously non-cystic kidney. Acquired cystic kidney disease (ACKD) may occur in any patient with ESRD. This includes children on dialysis, as well as those following renal transplantation when ACKD may infrequently occur in native kidneys left in situ. Although the number of cysts increase over time, children with ACKD are at a low risk for gross hematuria and retroperitoneal hemorrhage.[99] More ominously, a small percentage of children develop renal cell carcinoma. Because of this possibility, periodic ultrasound screening of all pediatric ESRD patients is necessary, and children with any suspicious lesions should have a nephrectomy.

Approach to evaluation

In some patients, the diagnosis of cystic kidney disease is straightforward. In other cases, diagnosis requires careful integration of laboratory, imaging, and clinical data. Occasionally, kidney or liver biopsy may be necessary in order to establish the diagnosis. The availability of genetic testing greatly improves diagnostic acumen in confusing cases. A diagnostic algorithm is provided in Figure 17.5, with the caveat that atypical presentations are not unusual in cystic kidney disease.

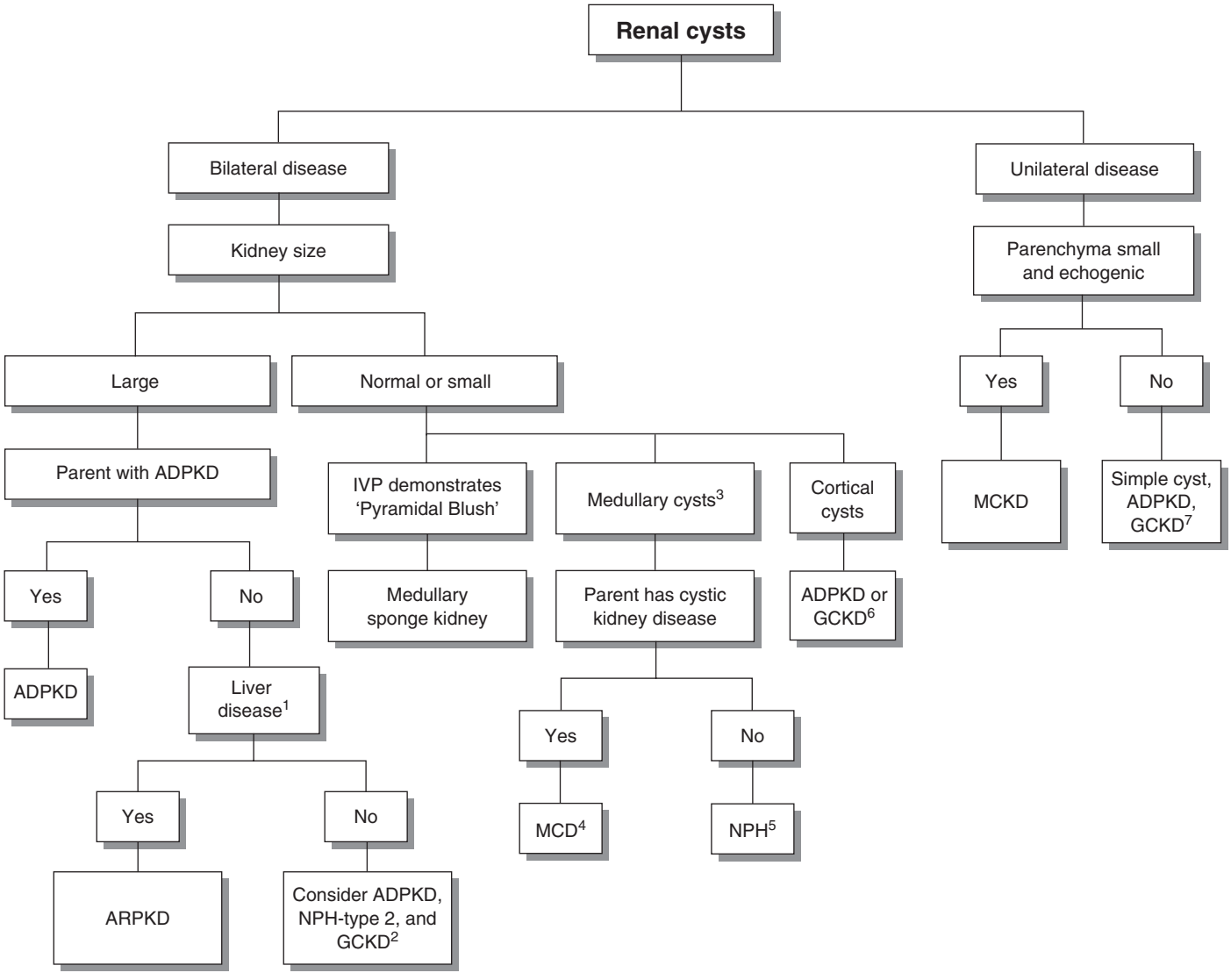

Figure 17.5 Diagnostic algorithm for the patient with suspected cystic kidney disease. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; NPH, nephronophthisis; GCKD, glomerulocystic kidney disease; IVP, intravenous pyelogram; MCD, medullary cystic disease; MCDK, multicystic dysplastic kidney.

1. Liver disease may be apparent on ultrasound, but a negative ultrasound does not eliminate hepatic disease. Only a biopsy is definitive. Hence, the absence of liver disease by ultrasound does not eliminate ARPKD.
2. ADPKD remains a diagnostic consideration due to non-paternity or a spontaneous mutation, which occurs in <5% of patients. The diagnosis can be confirmed by genetic testing. Consider the extremely rare NPH type 2 if the patient is an infant with renal failure. This diagnosis is more likely if there is a history of consanguinity or an affected sibling. Sporadic GCKD is an additional consideration.
3. Medullary cysts are not always visible by ultrasound with nephronophthisis (CT increases the detection rate). Cyst detection is even less common with medullary cystic kidney disease.
4. Confirm diagnosis with laboratory testing (hyperuricemia), genetic testing, and clinical history (renal failure typically occurs during adulthood).
5. Confirm diagnosis with clinical history (polyuria and chronic renal failure in childhood) or genetic testing. Definitive if tapetoretinal degeneration, but usually not present.
6. In ADPKD, cysts may be present throughout the parenchyma and a parent is usually affected. For GCKD, a parent may be affected, although cysts may only appear later in adulthood. Small echogenic kidneys and a patient or family history of early-onset type 2 diabetes is supportive of GCKD.
7. Simple cysts, which are uncommon under the age of 20 years, are a diagnosis of exclusion; more than 1 cyst is very unusual in childhood. ADPKD is suggested by a positive family history or the presence of liver, pancreatic, or splenic cysts (all are uncommon in children). With ADPKD, the number of cysts gradually increase and become bilateral; kidney size is normal or increased. Cysts in GCKD are cortical and often associated with echogenic parenchyma.

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18 Kidney in viral infections

Monique E Cho and Jeffrey B Kopp

Viral infections can cause a variety of renal diseases, which can lead to significant morbidity. Renal injury by human immunodeficiency virus (HIV-1), hepatitis B virus (HBV), and hepatitis C virus (HCV) has been well described. This chapter will review these three important viral pathogens and also include nephropathies related to human parvovirus B19 (PVB19) and Epstein–Barr virus (EBV).

Human Immunodeficiency virus-1

Epidemiology

In 1983, reports of the first cases of pediatric acquired immunodeficiency syndrome (AIDS) occurred in the United States.[1,2] AIDS was initially described in two age groups of pediatric population: infants infected through vertical transmission; children who acquired infection through blood transfusions. Subsequently, pediatric AIDS became a major public health concern worldwide, particularly in sub-Saharan Africa, where approximately 600 000 children are born with HIV-1 infection per year.[3] By the end of 2001 in the United States, pediatric AIDS cases represented approximately 1.2% of the total cases of AIDS, predominantly affecting minority populations. African-Americans comprise about 65% of all children with HIV-1 infection or AIDS, and more than 40% of these children have an increased prevalence of renal complications.[3–5]

Clinicopathologic variants

HIV-1 infection is associated with a variety of glomerular diseases:

- HIV-associated collapsing glomerulopathy (frequently referred to as HIV-associated nephropathy or HIVAN)
- HIV-associated glomerulonephritis (HIV-associated GN)
- HIV-associated thrombotic microangiopathy (HIV-associated TMA) (Table 18.1).[6–10]

Among African-American patients, collapsing glomerulopathy is the most common clinicopathologic disorder, whereas HIV-associated GN is most prevalent among Caucasian, Hispanic, and Asian patients. During the early years of the AIDS epidemic in children, Strauss et al[4] estimated the prevalence of childhood HIV-associated collapsing glomerulopathy to be approximately 10–15%. These data were based on clinical criteria and/or histology from studies of predominantly African-American pediatric patients.

Table 18.1 Glomerular diseases associated with viral infections

Infection	Disease
HIV-1	Collapsing glomerulopathy Glomerulonephritis: lupus-like, membranoproliferative, IgA nephropathy Other: membranous nephropathy, fibrillary and immunotactoid nephropathy, and thrombotic microangiopathy
HBV	Membranous nephropathy – most common in children Membranoproliferative glomerulonephropathy IgA nephropathy Polyarteritis nodosa
HCV	Membranoproliferative glomerulonephropathy (with or without cryoglobulinemia)

HIV-associated collapsing glomerulopathy

Clinical manifestations and background

Patients with HIV-associated collapsing glomerulopathy often present with asymptomatic proteinuria and are usually normotensive. Renal ultrasound classically shows enlarged, echogenic kidneys. Although HIV-associated collapsing glomerulopathy can occur at any stage of the disease, including the time of seroconversion, it is most commonly seen in patients with advanced HIV disease.[11] In the initial years of the HIV epidemic, this syndrome was characterized by a rapid progression to end-stage renal disease (ESRD). Further, these patients also had increased mortality on dialysis. Abbot et al, using the data from United States Renal Data System (USRDS), showed that 2-year survival was 36% for patients with HIV-associated nephropathy on dialysis, compared with 64% for those with ESRD of other etiologies between 1992 and 1997.[12]

Patients of African descent have striking susceptibility to developing HIV-associated collapsing glomerulopathy, with nearly 90% of the cases occurring in black individuals. Twenty five percent of patients with HIV-associated collapsing glomerulopathy have first-degree or second-degree family members with ESRD, suggesting a genetic predisposition to glomerular injury.[13] HIV-associated collapsing glomerulopathy is the third leading cause of ESRD in blacks aged 20–64 years old, after diabetes mellitus and hypertension.[7] Based on the USRDS, the relative risk for ESRD from HIV-associated nephropathy is approximately 18-fold increased among African-Americans compared with white patients.[14]

Pathology

The renal histology is characterized by segmental or global collapse and sclerosis of the glomerular tuft (Figure 18.1). Podocytes, which are normally postmitotic cells, re-enter the cell cycle and proliferate, in some cases forming pseudocrescents, and lose differentiation markers. There is tubular injury, with atrophy and microcyst formation (Figure 18.2).

Pathogenesis

The HIV-1 genome contains nine genes (*gag*, *pol*, *vif*, *vpr*, *vpu*, *rev*, *tat*, *env*, and *nef*) which encode 15 proteins. These viral accessory proteins have pleiotropic effects on cell function and are implicated in renal injury. Vpr induces G2 cell cycle arrest, perturbs mitochondrial functions, induces (and in some cells prevents) apoptosis, and alters gene transcription by acting as a coactivator. Roles of other accessory proteins in inducing renal injury have not been excluded. Tat and Nef each induce proliferation of podocytes, a distinctive feature of HIV-associated collapsing glomerulopathy.[15,16] A series of studies using transgenic mice bearing various portions of this genome have suggested which genes may be responsible for renal injury. HIV-1 transgenic mice carrying a replication defective HIV-1 provirus that lacks *gag* and *pol* develop renal disease characterized by podocyte dysplasia and proliferation, glomerular capillary tuft collapse, focal segmental glomerulosclerosis (FSGS), and tubular injury, and do so even in the absence of immunosuppression and viral replication.[17,18] Deletion of *nef* from the transgene reduced the severity of interstitial nephritis, but it did not prevent the development of glomerular disease in one transgenic line.[19] More recently, mice bearing *tat* and *vpr* or *vpr* alone developed FSGS.[20] These data from transgenic mice indicate that *vpr* induces FSGS and that *nef* contributes to interstitial nephritis.[20–22]

Because expression of HIV-1 gene products within podocytes and tubular epithelial cells can induce all the features of HIV-associated FSGS, the next question has been to understand how those gene products enter renal parenchymal cells. The data regarding direct infection of renal epithelium by HIV-1

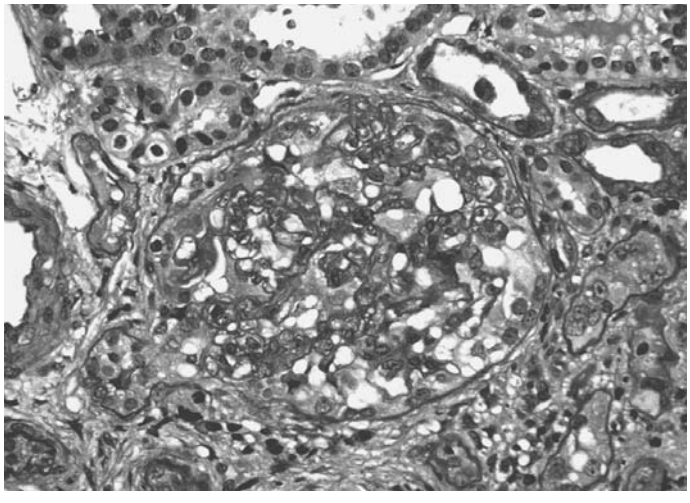

Figure 18.1 HIV-associated collapsing glomerulopathy in a 33-year-old patient. The light microscopy shows collapse of the glomerular tuft. Vacuolization and crowding of the glomerular epithelial cells are commonly seen and reflect the primary epithelial cell injury in this disease.

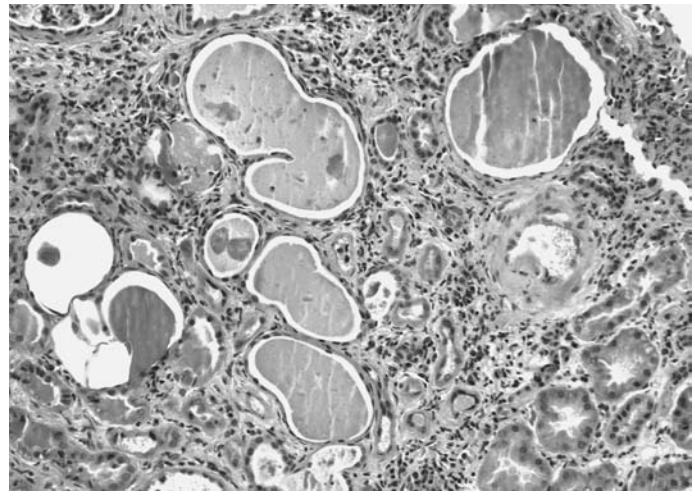

Figure 18.2 HIV-associated tubulointerstitial changes in a 20-year-old patient. The pathology includes asymmetric, occasionally massive, tubular epithelial cell cytoplasmic protein resorption droplets, acute tubular epithelial injury with focal simplification, and variable microcystic change.

have long been controversial. Bruggeman et al have, however, provided supportive evidence to suggest that HIV-1 viruses can directly infect the renal tissue. They detected HIV-1 in the renal tissue by RNA in-situ hybridization and DNA in-situ polymerase chain reaction.[23] HIV-1 RNA was detected in renal tubular epithelial cells, glomerular visceral and parietal epithelial cells, and interstitial leukocytes. In addition, the distribution of HIV-1 infection of renal tubules is similar to the pattern of microcystic tubular disease, a prominent histologic feature of the nephropathy. This correspondence further supports the direct infection of renal parenchyma by the HIV-1 virus.[24]

Infection of renal epithelial cells by HIV-1 has another important implication: the kidney may serve as a reservoir for HIV-1. Marras et al have detected variation in the HIV-1 envelope sequences in the renal tubular epithelium of HIV-infected patients, indicating that renal epithelium can support viral replication.[25] Furthermore, the envelope sequences of HIV-1 found in renal epithelium were distinct from the sequences derived from the same patient's peripheral blood samples, suggesting that the renal epithelium is a distinct reservoir for viral replication from the blood.

Treatment

Although HIV-associated collapsing glomerulopathy is an important cause of renal failure in the United States, no randomized controlled trials have been carried out to assess various therapies. Thus, recommendations are based on retrospective or uncontrolled studies. It is likely that highly active antiretroviral therapy (HAART) prevents the onset or slows progression of HIV-associated collapsing glomerulopathy (based on the epidemiologic evidence of fewer cases reaching ESRD in recent years) and may reverse clinical manifestations (based on anecdotal reports).[11,26] Angiotensin-converting enzyme (ACE) inhibitors also have been shown to reduce proteinuria and progression of renal disease in HIV-infected patient.[27,28]

The role of immunosuppressive therapy is less clear. Studies using prednisone in patients with renal dysfunction and HIV-1 infection show some efficacy in preserving renal function and reducing proteinuria.[29,30] However, these studies are not well controlled and not all reported patients underwent renal biopsy. Another retrospective study suggested efficacy of combination therapy with HAART and glucocorticoid.[31] The mean renal survival to ESRD was 26 months for those treated with the combination therapy, 6 months for those given HAART alone, and 3 months for those given neither HAART nor glucocorticoid. Although no studies have suggested efficacy of glucocorticoid in children with HIV-associated collapsing glomerulopathy, a very small study reported remission of proteinuria with cyclosporine therapy in three children who had steroid-resistant renal disease.[32] Again, the study was not a controlled trial and was done before the era of HAART, making it difficult to draw any conclusion.

More recently, the potential therapeutic role of cyclin-dependent kinase (CDK) inhibitors has been examined. CDK inhibitors were found to inhibit podocyte proliferation and induce re-expression of normal podocyte differentiation markers in vitro.[33] Gherardi et al have recently reported reversal of collapsing glomerulopathy in HIV-transgenic mice with CDK inhibitors.[34] This study demonstrates a potential new strategy in the treatment of HIV-associated collapsing glomerulopathy.

HIV-associated glomerulonephritis

In the absence of a national registry of renal biopsy finding, the true prevalence of HIV-associated GN is unknown. Several different histologic descriptions have been reported for HIV-associated GN, including a lupus-like pattern, membranoproliferative glomerulonephritis, membranous nephropathy, fibrillary and immunotactoid glomerulonephritis, postinfectious glomerulonephritis, and immunoglobulin A (IgA) nephropathy. It is not always possible to discern if the renal disease is a consequence of the HIV-1 infection or if it is a coincidental occurrence. For example, patients with HIV disease are often co-infected with hepatitis B or hepatitis C, each of which can be associated with glomerular diseases, such as membranous glomerulopathy and membranoproliferative glomerulonephritis.

The pathogenesis of these forms of HIV-associated GN is not clear. In IgA nephropathy, immune complexes containing HIV proteins have been found in the mesangium, possibly delivered from plasma, or forming in situ, leading to renal parenchymal inflammation.[35] Guidelines for treatment are limited by the lack of prospective, randomized controlled trials, but therapies have included antiretroviral therapy, ACE inhibitors, and prednisone.[36,37]

Thrombotic microangiopathy

Since the first report of HIV-associated thrombotic microangiopathy (TMA) in 1984, it has been increasingly recognized as a common microvascular injury in this infection.[38] A retrospective study demonstrated that 15 of 224 AIDS patients (7%) had evidence of TMA at the time of death.[39] The pathologic findings include occlusive thrombi in small arteries and arterioles, and detachment of glomerular endothelial cells from the basement membrane (Figure 18.3). Affected patients typically present with hemolytic uremic syndrome characterized by renal insufficiency, microangiopathic hemolytic anemia, and thrombocytopenia. The pathogenesis of TMA involves endothelial injury caused by toxins, vasoactive peptides, or immune factors. Infection of microvascular endothelial cells by HIV-1 has not been confirmed and the mechanisms that induce microvascular damage in HIV-1 infection are poorly understood. There are no data to suggest that HIV-associated TMA should be treated differently from idiopathic or autoimmune forms of TMA. Therapies have included plasmapheresis and/or prednisone, with limited success in HIV-associated TMA.

Drug-induced nephrotoxicity in HIV infection

Drug-induced acute renal failure, with or without chronic progression, is a common cause for renal insufficiency in the

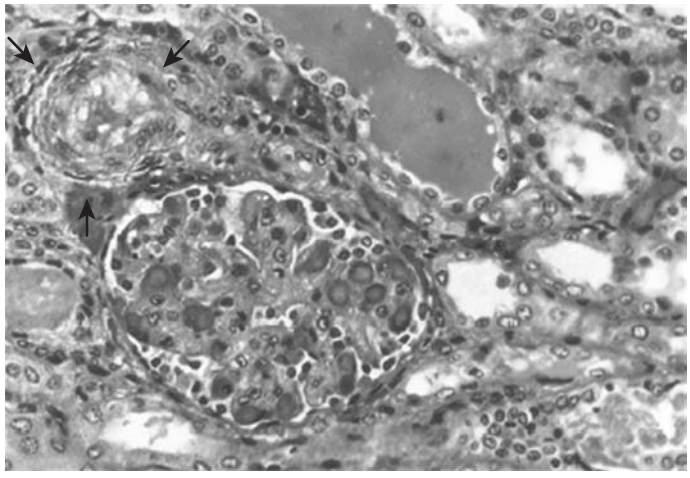

Figure 18.3 Light microscopy of renal biopsy in a child with HIV-associated thrombotic microangiopathy. The glomerular capillaries are collapsed and red blood cell fragments are present in several capillary loops. Arrows outline an arteriole with endothelial swelling and luminal narrowing due to thrombosis. (Reproduced with permission from Pediatr Nephrol 11:161, 1997.)

Table 18.2 Reported renal toxicity of tenofovir

Presentation	Fanconi syndrome Hypokalemia Proteinuria (usually <3 g/day) Diabetes insipidus (rare) Nephritic syndrome (rare)
Onset	2 weeks to 16 months
Renal biopsy	Acute tubular necrosis involving mostly proximal tubules
Risk factor	Concurrent use of lopinavir/ritonavir

HIV population. Examples include acute tubular necrosis due to pentamidine, foscarnet, cidofovir, amphotericin B, and aminoglycosides. Acute renal failure may also result from crystal precipitation following the use of sulfadiazine or intravenous acyclovir. Indinavir may cause renal calculi and obstruction.

More recently, case reports have described renal toxicity of tenofovir (Table 18.2), a newer nucleoside reverse transcriptase inhibitor (NRTI).[40–46] The patients had been taking tenofovir at daily doses of 300 mg for varying periods, ranging from 2 weeks to 16 months, when they developed renal failure. The renal toxicity is predominantly characterized by proximal tubular dysfunction, demonstrated by normoglycemic glycosuria, proteinuria, hematuria, and hypophosphatemia. Some patients also developed signs of distal tubular toxicity, presenting with diabetes insipidus.[40,43] The proteinuria associated with tenofovir is usually mild, but nephrotic-range proteinuria has also been described.[46] Continued administration of tenofovir may lead to chronic kidney disease in some patients. Renal function improves in most patients upon discontinuation of the drug, but persistent glycosuria and proteinuria with elevated creatinine, suggesting irreversible damage, has been documented in some cases. Renal biopsy in these patients has shown acute tubular necrosis, particularly involving proximal tubules

Tenofovir, an acyclic nucleoside phosphonate (ANP), belongs to a unique class of nucleoside analogs, which also includes cidofovir and adefovir. Much of the adverse effects associated with NRTIs have been attributed to mitochondrial toxicity, as phosphorylated forms of some NRTIs are potent inhibitors of mitochondrial DNA polymerase.[47] Drug-related deficiencies in the mitochondrial oxidative phosphorylation system lead to disruption in pyruvate oxidation and increased lactic acid production. Thus, organs rich in mitochondria, such as muscle, liver, and kidney (particularly proximal tubules), are at increased risk for the clinical toxicities, which can manifest as myopathy, liver steatosis, lactic acidosis, and Fanconi syndrome. ANPs undergo renal tubular secretion through proximal tubules (via human renal organic anion transporter-1). Therefore, the accumulation of the drug in the proximal tubules probably plays an important role in nephrotoxicity. Given the possible nephrotoxicity, patients taking tenofovir (especially those also on lopinavir/ritonavir, which can increase the serum concentration level of tenofovir) need to be monitored regularly. The decision regarding when the drug should be stopped needs to be individualized.

Hepatitis B virus

Chronic hepatitis B (HBV) infection is a global public health problem affecting approximately 350 million people, or 5% of the world's population. The prevalence of HBV carriers varies from <1% in non-endemic areas (North America, Western Europe, Australia, and New Zealand), to 3–5% in intermediate areas (Mediterranean countries, Japan, Central Asia, Middle East, and Latin and South America), and to 10–20% in endemic areas (southeast Asia, China, and sub-Saharan Africa).[48]

In non-endemic areas, HBV infection is predominantly a disease of adults, being transmitted largely through intravenous drug use or sexual contact. In the endemic countries, however, HBV is a common disease of childhood, with either vertical or horizontal transmission. This difference in the age at initial infection is likely to be responsible for the wide variability in prevalence of chronic HBV infection in different parts of the world.

The risk of chronicity in HBV infection is inversely related to the age at infection.[49] The risk of chronic infection in infants <1 year of age is thus as high as 90% compared with 10–40% at 4–6 years and 1–5% in adults. Given that the majority of HBV infection occurs during the first year of life in many endemic areas, it is not surprising that the burden related to the complications of chronic HBV infection is also highest in these areas.

Clinicopathologic variants

Various clinicopathologic forms of renal diseases have been described in patients with chronic HBV infection. These include membranous nephropathy, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, IgA nephropathy, and polyarteritis nodosa (see Table 18.1).[49,50] Although there have also been reports of lupus nephritis, FSGS, and minimal change nephrotic syndrome, it is unclear if these were incidental findings. The most widely accepted pathogenesis for HBV-associated renal disease is the deposition of immune complexes of viral antigen and host antibody.

Membranous nephropathy

Membranous nephropathy is the most common form of HBV-associated nephritis in children, accounting for >85% of HBV-associated renal disease undergoing renal biopsy. HBV envelope antigen (HBeAg) is believed to be the primary antigen present in the subepithelial deposits.[51] Approximately 30–60% of children with HBV-associated membranous nephropathy (HBV-associated MN) undergo spontaneous remission, usually in association with development of anti-HBeAg seroconversion, over 6–24 months.[52] In a study of 71 children with HBV-associated MN from Cape Town, the average time of clearance of HBeAg to remission was 5 months.[50] This is in contrast to adults, who tend to develop progressive nephropathy in about 25% of the affected individuals. The presentation of HBV-associated MN also differs between pediatric and adult patients. Whereas adults tend to present with nephrotic syndrome, children can remain asymptomatic and the proteinuria may be incidentally discovered during a routine urine and serologic screening. In addition, there is a stronger male predominance in children affected by HBV-associated MN and children are also less likely to experience acute hepatitis compared with adults.[49]

Mesangial proliferative glomerulonephritis

Chronic HBV infection has also been associated with mesangial proliferative glomerulonephritis with deposition of IgA and HBV surface antigen in the mesangium.[53] Bhimma et al reported that 6 of 23 children with HBV-associated nephropathy other than membranous disease had mesangial proliferative glomerulonephritis.[54] It is unclear if the deposited IgA has anti-HBV surface antibody activity.

Membranoproliferative glomerulonephritis

HBV-associated membranoproliferative glomerulonephritis (MPGN) is characterized by the deposition of antigen–antibody complexes in the mesangium and subendothelial space. These glomerular deposits are mainly composed of IgG and C3 and both HBV surface and envelope antigens have been implicated in this glomerulonephritis. MPGN typically occurs in association with mixed cryoglobulinemia, particularly in the setting of coinfection with HCV.

Polyarteritis nodosa

Polyarteritis nodosa, a large-vessel vasculitis that also results from antigen–antibody complex deposition in the vessels, can be associated with HBV infection.[55] The clinical presentation is comparable to polyarteritis that is not associated with HBV and typically occurs within 4 months of the onset of HBV infection.

Treatment

Therapy for HBV renal diseases has focused on antiviral therapies, although the data from controlled studies are limited. In general, immunosuppression for HBV-associated renal disease is of no proven benefit, particularly in children with membranous nephropathy in whom spontaneous recovery over 6–24 months is common.

Antiviral therapies

Currently, the three medications approved for treatment of chronic HBV infection in adults are interferon-α, lamivudine, and adefovir dipivoxil. Of these, interferon-α and lamivudine are approved for use in children in the United States. Several controlled trials in children with HBV infection have evaluated the efficacy of interferon-α in different parts of the world. Response rate, defined as HBeAg seroconversion or disappearance of plasma HBV DNA, tends to be highest in Western countries, at 20–58%[56–58] and lower in Asian countries at about 17%.[59,60] The difference in response rates may not be due to ethnicity but rather to the fact that a higher proportion of patients from endemic areas are infected at birth and are in the immune-tolerant phase of infection. It is unclear why such patients are less likely to respond to antiviral therapy. Based on current data, interferon-α may be an effective therapy for HBV-associated MN, particularly in young children in non-endemic areas.

Experience with lamivudine in children with chronic HBV infection is limited. Although the available data suggest its efficacy and safety in children, the benefit of lamivudine must be balanced against the risk of selecting resistant mutants. Children with higher baseline alanine aminotransferase and histologic activity index scores on liver biopsy are more likely to respond to lamivudine.[61] The optimal duration of therapy is unclear. Lamivudine should be used for at least 1 year, and continued for at least 6 months after HBeAg seroconversion. Adefovir has been evaluated as monotherapy for adults with chronic HBV infection and those who have developed resistance to lamivudine. Other potential antiviral agents that require further studies in children include pegylated interferon, famciclovir, and lobucavir.

Immunosuppression

Glucocorticoids or cytotoxic agents, which are used in primary membranous nephropathy, have no proven benefit in patients with HBV-associated MN.[62] Indeed, immunosuppression may lead to greater viral replication and exacerbation of chronic hepatitis. One exception may be in patients with active vasculitis,

who may require a short course of steroid treatment to control the inflammatory response.[63]

Immunoprophylaxis

The most important strategy to improve morbidity and mortality associated with chronic HBV infection is immunoprophylaxis. HBV vaccination given as part of routine immunization in endemic areas is highly effective in reducing the incidence of HBV-associated MN.

Hepatitis C virus

HCV infection, the leading indication for liver transplantation, remains a significant cause for morbidity and mortality in adults. It is, however, a less common cause of liver disease in children. In the United States, 60 000 to 100 000 children (0.2–0.4% of all children) are estimated to have chronic infection with HCV, although the specific incidence in children is unknown.[64] The prevalence is much higher in children (50–95%) who received multiple transfusion of blood and blood products before 1992.[65]

The predominant route of HCV infection in children is perinatal transmission. The incidence of vertical transmission of HCV is approximately 2–5% in HCV RNA positive mothers, but coinfection with HIV-1 can more than quadruple the risk to about 20%.[66] Among adolescents, risk factors also include intravenous or intranasal drug use and use of contaminated tattoo instruments.

The natural history of HCV in the pediatric population is incompletely understood. In general, infections acquired early in infancy (either by transfusion or vertical transmission) are more likely to undergo spontaneous clearance than infections acquired later in life, and the actual reported rates have been variable, from 9 to 45%.[67–69] Another general observation is that HCV is often mild and less progressive during childhood.

HCV nephropathy

The predominant glomerular disease associated with HCV is MPGN, usually in the setting of cryoglobulinemia. Other forms of glomerular disease associated with HCV in adults include membranous nephropathy,[70] and fibrillary and immunotactoid glomerulonephropathy.[71] Unlike HBV, renal disease is rare in children with HCV, usually occurring in those with long-standing infection. In one report, the estimated time from HCV infection to diagnosis of renal disease was greater than 15 years.[72] Despite this mild clinical course of HCV infection in children, it is unknown if these patients will continue to have a benign course in the future. To date, no studies have examined whether treatment of children with HCV infection reduces their subsequent risk of cirrhosis, hepatocellular carcinoma, or renal complications. There are no systemic studies of HCV-associated nephropathy in children.

Clinical manifestations

Patients with MPGN may present with nephrotic or subnephrotic proteinuria and hematuria, with variable degree of renal insufficiency. Cryoglobulins are detected in 50–70% of patients. Those patients with cryoglobulinemia may also present with palpable purpura, arthralgia, and neuropathy. Patients with MPGN will often have elevated serum aminotransferase levels, with the majority having rheumatoid factor and low complement levels.

Pathology

The predominant glomerular disease associated with HCV is MPGN (Figure 18.4), usually in the setting of cryoglobulinemia. Histopathologic examination shows typical changes associated with MPGN, including lobular glomeruli, increased mesangial cellularity, and intracapillary accumulations of eosinophilic material representing precipitated immune complexes or cryoglobulins.[73] Electron microscopy shows subendothelial immune complex deposits (Figure 18.5) and may have a finely fibrillary or tactoid pattern characteristic of cryoglobulin deposition. Although the pathogenesis of glomerular injury in HCV is unclear, it is believed to result from deposition of circulating immune complexes of HCV, anti-HCV, and rheumatoid factor at the site of injury.

Treatment

The therapy for renal diseases associated with HCV, particularly MPGN, focuses on treatment with antiviral agents. A few small and non-randomized studies have evaluated the efficacy of the combination therapy in HCV-associated MPGN with interferon-α and ribavirin.[72,74–77] In general, these studies have

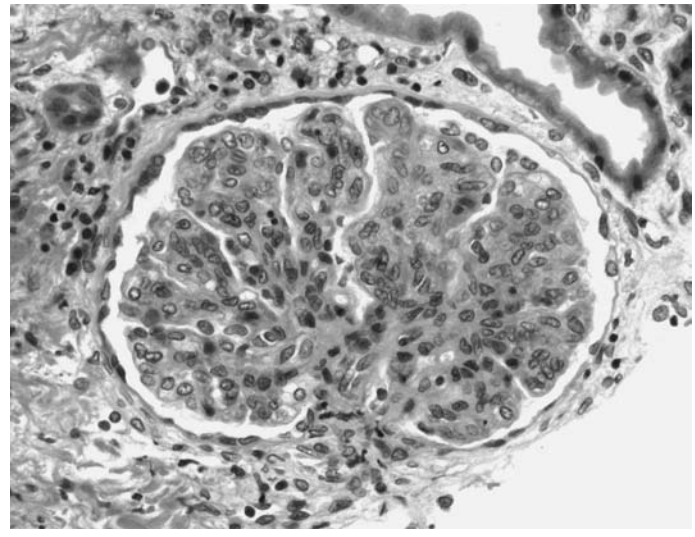

Figure 18.4 Light microscopy of hepatitis C virus-associated membranoproliferative glomerulonephritis in a 15-year-old patient. The glomerular tuft has a lobular appearance with focal areas of increased glomerular cellularity and mesangial expansion.

suggested efficacy in lowering or clearing viral titers, improving clinical symptoms (related to cryoglobulinemia), and decreasing proteinuria, with variable impact on renal function.

Although there are no reports of intervention in children with HCV-associated nephropathy, a recent open-label uncontrolled 48-week study in children with chronic HCV infection has suggested efficacy and safety of the combination therapy with peginterferon and ribavirin.[78] The authors found that 22 of 46 (48%) patients with genotype 1 and 13 of 13 patients (100%) with genotype 2 or 3 achieved sustained viral suppression. Further prospective controlled studies are necessary to determine if this combination therapy will improve long-term morbidity and mortality for children and whether it will prevent development of glomerulonephropathy. Patients who do not respond to the combination therapy or those who have contraindications may be candidates for an investigational treatment with rituximab, an anti-CD20 chimeric monoclonal antibody. Two preliminary observational studies in 10 patients have been encouraging.[79,80]

For more severe or acute cryoglobulinemic renal disease or systemic vasculitis, antiviral therapy does not seem to prevent progression of renal injury.[81] In such cases, combination therapy with anti-inflammatory and cytotoxic drugs may be necessary in order to prevent new antibody formation. Plasmapheresis is also frequently used in conjunction to remove the circulating cryoglobulins. Although there are no controlled trials, observations suggest that this regimen may lead to improvement in renal function in over 50% of patients.[81,82]

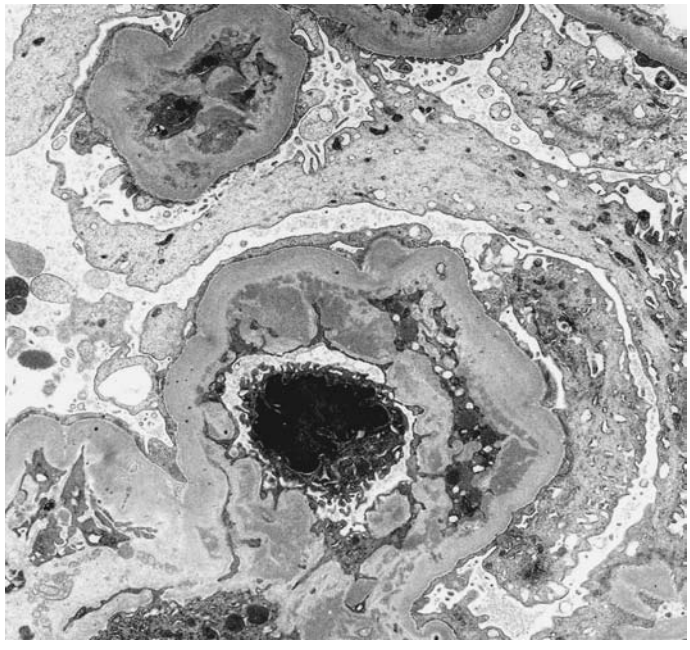

Figure 18.5 Electron micrograph of HCV-associated type I membranoproliferative glomerulonephritis. The glomerular capillary wall is markedly thickened with immune deposits and by interposition of mesangial cell processes.

Table 18.3 Renal manifestations of human parvovirus B19

Presentation	Acute nephritic syndrome Hypocomplementemia Proteinuria
Onset	2 weeks (3–45 days) after infection
Renal biopsy	Mesangial proliferative glomerulopathy Thrombotic microangiopathy Focal segmental glomerulosclerosis Collapsing glomerulopathy

Human parvovirus B19

Human parvovirus B19 (PVB19), a single-stranded DNA virus discovered by an Australian virologist Yvonne Cossart in 1975,[83] is the only parvovirus clearly linked to human disease. In 1993, Brown et al discovered that the receptor for PVB19 is blood group P antigen or globoside (Gb4). This explains the primary tropism of PVB19 for erythroid precursors.[84] Gb4 is also expressed in other cell types, such as lung, heart, liver, kidneys, synovium, endothelium, and vascular smooth muscle.[85] PVB19 is the etiologic agent of erythema infectiosum or fifth disease, a highly contagious childhood exanthem. PVB19 has also been implicated in a wide spectrum of diseases, including polyarthropathy, acute aplastic crisis (particularly in patients with increased erythropoiesis), chronic anemia (in immunocompromised hosts), and hydrops fetalis.[86] In addition, PVB19 has been increasingly reported in association with various renal diseases (Table 18.3).

Acute glomerulonephritis and thrombotic microangiopathy

The most frequently reported renal disease in PVB19 infection is acute postinfectious glomerulonephritis (AGN). Nineteen cases of PVB19-associated AGN have been reported to date in children and adults without any underlying diseases.[87–95] PVB19-induced AGN typically occurs within 2 weeks (range 3–45 days) of the viral infection. Usual presentation is with acute nephritic syndrome and hypocomplementemia.

The histopathologic description of PVB19-induced AGN includes endocapillary and/or mesangial proliferative glomerulonephritis. Immunofluorescence typically shows granular deposition of C3, IgG, and/or IgM along capillary walls and in the mesangium. Electron microscopy may demonstrate subendothelial electron-dense deposits; subepithelial deposits are generally absent. Immunohistochemical analysis using monoclonal antibody against PBV19 antigen has shown positive staining along capillary walls and in the mesangium, suggesting that the immune complexes with PVB19 may be implicated in the development of AGN.[87,90,91] The diagnosis of acute

PBV19-associated GN is suggested by immunostaining of kidney tissue and specific IgM antibody and plasma PCR (polymerase chain reaction) detection of the viral genome.

Renal biopsies of some patients with PBV19-induced AGN also had features consistent with TMA, including subendothelial widening, mesangiolytic changes, and thrombotic lesions (Figure 18.6).[88,90] Although the exact pathogenesis is unknown, PBV19 may cause endothelial injury by an immune complex-mediated mechanism and by direct cytotoxicity of the endothelial cells. The observation that the vascular endothelial cells express PVB19 receptor suggests that the virus may directly infect and injure endothelial cells.[85] PBV19 infection has been associated with TMA in four renal allograft recipients and in a healthy adult.[96,97] Given that PVB19 may cause renal injury through various pathways, AGN and TMA may represent phenotypic variants of the same disease, rather than two distinct pathologic entities.

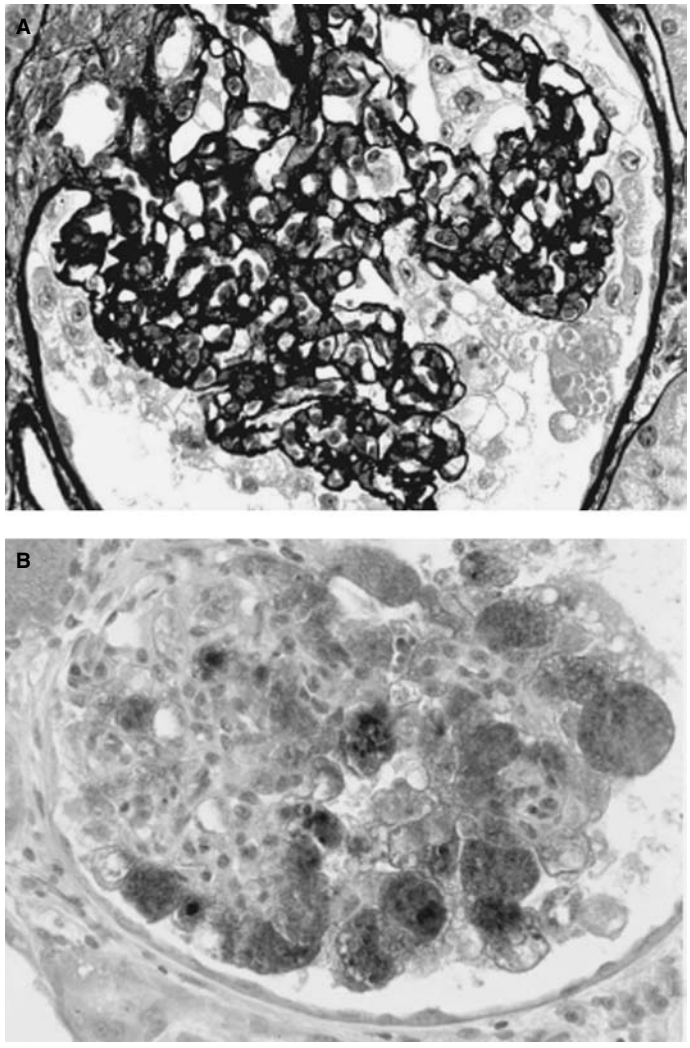

Figure 18.6 Photomicrograph of a glomerulus from a patient with early human parvovirus B19 (PVB19)-associated collapsing glomerulopathy. (A) Podocytes are enlarged with cytoplasmic vacuoles and protein reabsorption droplets. Capillaries are obliterated due to collapse of the walls, and mononuclear leukocytes are spread in the capillary lumens. (B) PVB19 immunostaining reveals viral protein within the enlarged podocytes.

Treatment

Most of the patients with PVB19-induced AGN recovered spontaneously without any specific treatment. Clearance of PVB19 and fall of IgM titers usually take about 8 weeks following the initial infection. Low titers, however, may persist up to 6 months and some patients may not show full recovery for 6 months. The therapy for patients with no underlying medical conditions thus remains supportive. For immunocompromised hosts or those with persistent symptoms, intravenous immunoglobulin may be considered. Successful treatment of chronic PVB19 infection with intravenous immunoglobulin therapy has been reported in patients with lymphoma,[98] acute PVB19-induced myocarditis,[99] PVB19-induced chronic fatigue syndrome,[100] and recurrent PVB19 infection with collapsing glomerulopathy in a renal transplant patient.[101]

Focal segmental glomerulosclerosis and collapsing glomerulopathy

The initial cases of FSGS in patients with PVB19 infection were observed in patients with sickle cell disease. Markenson et al first described the link between renal disease and PVB19 in two siblings with sickle cell disease who developed nephrotic syndrome following PVB19-induced aplastic crises.[102] Wierenga et al also described a similar report in seven patients with sickle cell disease presenting with nephrotic syndrome following PBV19 infection.[103] The renal biopsy performed during the acute phase in four patients revealed segmental proliferative glomerulonephritis without significant immune complex deposition. In the fifth patient who underwent renal biopsy 4 months following the onset of symptoms, the diagnosis of FSGS was made. Tolaymat et al reported a similar pediatric case of FSGS and established the first direct association between glomerular disease and PVB19 by demonstrating the viral DNA in renal specimen by PCR.[104] Tanawattanacharoen et al examined PVB19 DNA in renal biopsy specimens and found that the prevalence of the viral DNA was greater among patients with idiopathic FSGS and collapsing FSGS (85%) than other glomerular diseases (54%).[105] Similarly, Moudgil et al also reported 78% prevalence of PBV19 DNA in renal biopsies of patients with collapsing glomerulopathy as compared with the prevalence of 26% in controls.[106]

The renal prognosis of patients developing FSGS in the setting of sickle cell disease remains guarded. Among the seven patients reported by Wierenga et al, only one recovered completely, one reached end-stage renal disease within 3 months and died, and the rest of them had persistently impaired creatinine clearance, four with proteinuria.[103] Since

sickle cell disease itself is associated with post-adaptive FSGS, it is unclear how much of the progression of the renal disease in these patients is directly attributable to PVB19 infection. The benefit of immunosuppressive therapy in these patients also remains unclear, and the management needs to be individualized, with frequent monitoring and aggressive control of other renal risk factors such as hypertension and avoidance of nephrotoxins.

Epstein-Barr virus

Whereas the most common clinical presentation with EBV infection is infectious mononucleosis in adolescents and adults, most EBV infections are asymptomatic or non-specific in infants and children.[107] The diagnosis of EBV infection in children is challenging, not only due to its atypical presentation but also due to the fact that EBV serology in children differs from that in adults or adolescents. First, heterophil antibodies are rarely seen in young children. Secondly, although IgM antibody to EBV capsid antigen is considered to be a reliable marker of the infection, it is detected by the conventional indirect immunofluorescence method in a limited number of children.[108] Thirdly, antibody to EBV nuclear antigen (anti-EBV NA IgG), a late-onset antibody, tends to develop earlier in children than in adults.[109] Therefore, detection of anti-EBV NA IgG does not rule out the possibility of acute EBV infection in children.

Clinical manifestations

Mild renal involvement in EBV infection may be present in approximately 16% of patients with infectious mononucleosis.[110] Acute renal failure in patients with EBV infection is rare, and its incidence has been reported to be 1.6% in one study, although this rate may be higher in more severely affected individuals.[110] In a recent retrospective study of 165 Taiwanese children hospitalized with serologically proven primary EBV infection, Tsai et al reported that 8 had acute renal failure (4.8%).[111] Fever was the most common presentation in these eight children, with the classic triad of fever, pharyngitis, and lymphadenopathy being present only in one patient. Specific renal manifestations included bilateral flank pain and evidence of tubular damage, such as microscopic hematuria, mild proteinuria, glycosuria, or poor concentrating ability on urinalysis (Table 18.4). The creatinine levels typically peaked within 3 weeks following the clinical onset (range 3–17 days) in this study. Except for one patient who died of gastrointestinal bleeding, the remaining seven children recovered their renal function within 1 week to 1 month.

Table 18.4 Renal manifestation of Epstein–Barr virus-associated nephropathy

Presentation	Bilateral flank pain
	Tubular dysfunction: microscopic hematuria, mild proteinuria, Fanconi syndrome, urinary frequency due to impaired urine-concentrating ability
Onset	3–17 days following clinical onset
Renal biopsy	Tubulointerstitial nephropathy

Pathology

The most common pathologic abnormality in renal failure associated with EBV infection is acute tubulointerstitial nephritis. Other reported forms of EBV-associated renal disease are distinctively rare and include immune complex glomerulonephritis,[112] minimal change disease,[113] and hemolytic uremic syndrome.[114] Although the pathogenesis of EBV-associated interstitial nephritis remains enigmatic, Becker et al have postulated that EBV infection of renal proximal tubular cells may evoke cellular immune response that leads to interstitial damage.[115] Using in-situ hybridization and the PCR, these authors detected EBV DNA exclusively in the renal tissue of patients with idiopathic chronic interstitial nephritis.[115] The EBV genome was detected primarily in renal proximal tubular cells. Moreover, the authors detected the CD21 antigen, the receptor for EBV in B lymphocytes, also on proximal tubular cells, and this was significantly up-regulated with EBV infection. The authors speculate that induction of interstitial nephritis by EBV may be the consequence of cellular immune response by infected proximal tubular epithelial cells.

Treatment

The role of glucocorticoid therapy remains unclear in the treatment of patients with complications of EBV infection. Therapy with glucocorticoids has led to variable results. In the absence of data derived from controlled studies, specific guidelines regarding indications for glucocorticoid use in EBV-associated interstitial nephritis are difficult to formulate. Likewise, there is no conclusive evidence regarding efficacy of acyclovir to improve outcome or prevent complications in EBV infection.

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19 Sickle cell nephropathy

Jon I Scheinman

The clinical consequences of sickle cell disease (SCD) result from obstruction of microvascular circulation by the sickled cells and red cell hemolysis. Renal consequences of SCD can be subtle in the form of tubular concentrating defect, or as the dramatic onset of hematuria from renal papillary necrosis (RPN). A schematic representation of the timeline of the renal manifestations of SCD is given in Figure 19.1.

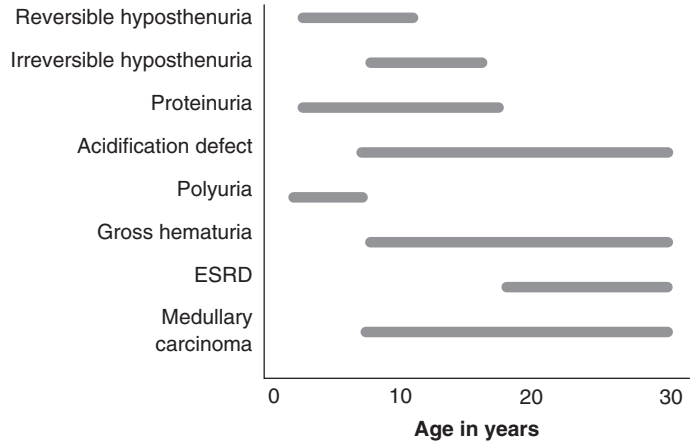

Figure 19.1 Age at onset of the renal manifestations of features in sickle cell disease. (Reproduced with permission from J Am Soc Nephrol 10:187, 1999.)

Epidemiology

SCD affects approximately 1% of the African-American population in the United States. The epidemiology of the renal-specific manifestations of SCD, especially its acute manifestations, has not been studied systematically. Sickle cell glomerulopathy with associated chronic kidney disease (CKD) and end-stage renal disease (ESRD) is a significant outcome of SCD. Overall, 5–18% of SCD patients develop CKD.[1]

Proteinuria is a common renal manifestation of SCD-associated renal disease, and nephrotic syndrome has been recognized in publications dating back to 1959.[2] In general, the prevalence of proteinuria is age-dependent, being lower in children and increasing with advancing age. Proteinuria was noted in 29% of adults and only 5% of children < 10 years of age in a single-center study of 284 patients.[3] In another single-center experience in children from the United States, the overall prevalence of dipstick proteinuria was noted to be 6.2% of SCD patients, but a higher prevalence was noted in older teenagers.[4] In our series, 87 (23%) of 381 adult SCD patients had significant proteinuria, and 12 (3.1%) had nephrotic range proteinuria (more than 2.5 g/24 h).[5] In another study of 34 selected adult patients with SCD, 7 had albuminuria with normal glomerular filtration rate (GFR) and 17 had chronic renal failure with glomerular injury and loss of ultrafiltration coefficient.[6] Lower GFR has been related to a lower hematocrit.[7] The incidence of proteinuria is higher in homozygous sickle cell disease (SS) and sickle-thalassemia (S-Thal) compared with heterozygous sickle cell trait (SA), whereas the incidence is in the intermediate range in sickle–hemoglobin C disease (SC).[8]

Hematuria as well as RPN are well-known clinical manifestations of renal disease in SCD. In one Nigerian series, 40% of SCD patients had urographic evidence of RPN.[9] Hematuria may not always be seen in patients with RPN, and many patients can be asymptomatic.[10]

Pathogenesis

Predisposition to renal involvement in SCD may be determined by various genetic factors that affect the level of fetal hemoglobin (HbF), as well as the intensity of sickling in each individual patient. However, the data regarding the role of various genes in such a predisposition are inconclusive. Powars et al reported the association of β-globin gene cluster haplotypes with renal involvement in SCD.[11] On the other hand, Guasch et al associated renal involvement with microdeletions in the α-globin gene.[12] In addition, factors that affect the interactions of red blood cells (RBCs) with endothelium may also be important in the pathogenesis of renal disease in SCD. The pathogenesis of renal disease in SCD is shown in Figure 19.2.

Hematuria

Hematuria in SCD is believed to be the consequence of renal medullary sickling, vascular obstruction, and injury. Sickling in the kidney is promoted by the acidic and hypoxemic milieu

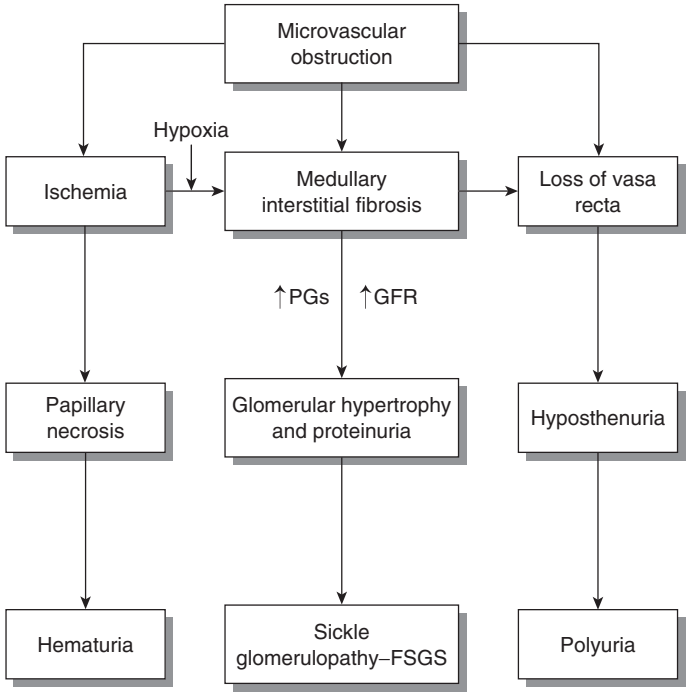

Figure 19.2 Pathogenesis of nephropathy in sickle cell disease. Modified and reproduced with permission from Saborio P and Scheinman JI. Sickle cell nephrology. J Am Soc Nephrol 1: 188, 1999.

(PaO_2 = 35–40 mmHg) of renal medulla.[13] High medullary osmolality, which facilitates osmotic draw of water from the RBCs, and concentrates hemoglobin S (HbS) in them, also adds to an environment that facilitates sickling. Hematuria can be seen in SS as well as heterozygous SA patients.

Urinary concentrating defect

Urinary concentrating ability depends upon an intact collecting duct. Continued low-grade sickling and medullary vascular congestion results in loss of the normal medullary concentration gradient necessary for water reabsorption.[14] Although defective urine concentrating ability can be transiently reversed by blood transfusion in early disease, medullary fibrosis and permanent collecting ducts destruction eventually results in an irreversible concentrating defect.[15–20] Vasopressin generation is normal in SCD, and the concentrating defect is not responsive to vasopressin.

The concentrating defect is unique to sickling among hemoglobinopathies.[20] Normal adults have the capacity to concentrate their urine to a mean maximal urinary osmolality of 1058 ± 128 mOsm/kg water. In homozygous sickle patients (SS), there is an impairment of the maximal urine concentrating capacity to a mean of 434 ± 21 mOsm/kg water.[20] This results in a relatively fixed low urine osmolality after 10 years of age. Concentrating defect, although also seen in SA and hemoglobin SC disease, is less severe in both.[20]

Urinary dilution depends on the solute reabsorption in the ascending loop of Henle of cortical nephrons, which are not involved in SCD patients. Therefore SCD patients can usually dilute the urine normally.[15]

Tubular dysfunctions

Urinary acidification is impaired in patients with SCD. Goossens et al noted that none of their patients with SCD were able to achieve a urine pH below 5.3, whereas normal controls were able to achieve a pH of 5.0.[21] Titrable acidity was lower but ammonia excretion was normal in patients with SCD. Electrolyte abnormalities resembling those seen in type IV renal tubular acidosis are seen in SCD result from an aldosterone-independent end-organ failure as a consequence of medullary fibrosis. Plasma renin and aldosterone concentrations may be increased, possibly as a protective mechanism against hyperkalemia and renal medullary fibrosis.[15]

Proximal tubular functions are supranormal in SCD. Increased proximal tubular sodium reabsorption in SCD results in less distal sodium delivery and a poor response to loop diuretics.[22] Proximal tubular phosphate reabsorption usually parallels sodium reabsorption and may cause hyperphosphatemia, especially in the presence of an increased phosphate load generated by hemolysis.[15] It is proposed that these alterations are adaptive, compensating for defects in medullary sodium and water conservation.[18] Tubular secretion of creatinine is increased in SCD. This leads to overestimation of creatinine clearance as a measure of GFR.[15] A disparity of up to 30% may be noted between creatinine clearance (C_{Cr}) and inulin clearance (C_{In}) in these patients.[15] Serum creatinine level is also lower in baseline conditions in SCD. The increased C_{Cr} observed normally after an intravenous creatinine load (by enhanced tubular secretion) is blunted in SCD, suggesting a lower renal tubular functional reserve.[23] These findings are believed to represent subclinical nephron mass reduction in SCD, even before the GFR is impaired.[23] Uric acid secretion is increased and may reflect a functional adaptation to high uric acid generation.[24] With decreasing total GFR and hyperfiltration, fractional excretion of urate is further increased by decreased reabsorption.[25]

Prostaglandins and sickle cell disease

Prostaglandins (PGs) have been implicated in the tubular dysfunction associated with SCD.[18,26] PGs normally facilitate an increased proximal sodium reabsorption. With PG inhibition, more solute is delivered to, and then reabsorbed from the thick ascending limb of the loop of Henle, thereby increasing interstitial hypertonicity. In turn, this results in a greater free water reabsorption in the relatively solute-impermeable descending limb and a decreased vasopressin suppressive response to water loading.[22] PG inhibition restores to normal (or decreases) the proximal sodium reabsorption in SCD, with a resultant decreased naturetic response to loop diuretics.[19]

While urinary dilution is not normally affected by PG inhibition, PG decreases urinary dilution capability in SCD.[22] SCD patients also fail to increase net acid excretion in response to inhibition of PG synthesis by indomethacin, possibly as a result of decreased NH_4^+ excretion.[27] It is also likely that NH_4^+ excretion is maximally maintained under the influence of endogenous PGs in SCD.

Hyperfiltration in sickle cell disease

Hyperfiltration and elevated GFR have long been recognized in patients with SCD, especially in children.[18] Renal plasma flow (RPF), as estimated by *p*-aminohippurate (PAH) clearance, is elevated in excess of GFR, resulting in a lower than normal filtration fraction (12.9 vs 17.5).[22] The dramatically increased RPF and decreased filtration fraction of SCD are returned to toward normal following PG inhibition. Both hyperfiltration and proximal tubular 'hyperfunction' in SCD may represent compensatory responses to the distal tubular injury, and PG systems could be implicated in their pathogenesis.[18,19]

Sickle glomerulopathy

In the past, glomerulopathy seen in SCD has been regarded as an immune complex disorder, mediated by injury and antibody response to the renal tubular epithelial cell antigen complexes.[18] However, most now agree that evidence of glomerular immune complex deposition is lacking in SCD patients with heavy proteinuria. The pathologic findings in sickle cell nephropathy resemble those of the rodent model of glomerular hypertension induced by renal mass reduction.[28] The uninvolved glomeruli have larger than normal diameters, while morphologic lesions of focal segmental glomerulosclerosis (FSGS) may be present in others.[4] The pathogenetic mechanism for development of the FSGS in SCD is believed to be hyperfiltration. Direct endothelial damage induced by glomerular capillary occlusion by the sickled red cells may also be responsible for endothelial hyperplasia and glomerular fibrosis.[13,18] Growth-promoting hormones and cytokines may play an important role in FSGS associated with hyperfiltration.[27–30] It is also possible that FSGS is the consequence rather than the cause of interstitial fibrosis by being a factor in the efferent glomerular capillary obstruction, resulting in raised intraglomerular pressure (glomerular hypertension) and progressive (reactive) glomerulosclerosis.[31]

Iron overload

The iron deposited as hemosiderin in the tubular cells has been suspected of playing a role in the chronic nephropathy of SCD.[32] Experimentally, saturated iron complexes can induce a nephrotic syndrome in rabbits.[16] Lande et al found a decreased renal cortical spin-echo signal by magnetic resonance imaging (MRI) in SCD, suggesting an abnormal renal cortical iron metabolism which is not observed to occur in β-thalassemia, despite similar iron overload.[33]

Tumorogenesis

It has been hypothesized that the medullary hypoxia in SCD predisposes to the distinctive renal medullary carcinoma.[34] Previously, it was noted that RPN itself predisposes to uroepithelial tumors.[35]

Pathology

Papillary necrosis

The renal pathology of SCD associated with isolated hematuria shows relatively insignificant changes: primarily, medullary congestion and sickled cells may be seen in glomeruli as well (Figure 19.3).[17] RPN is a focal process characterized by dilation and engorgement of vasa rectae by the sickled RBC, followed by repeated small focal papillary infarctions.[36] Medullary fibrosis follows, and few collecting ducts survive within this area of a diffuse fibrosis.[18] In some cases, acute ischemia of the papillae may result in their sloughing off and leading to gross hematuria and the presence of 'clots' in the urine. Examination of the 'clots' reveals their true nature as being renal papillary tissue. Acute urinary tract obstruction can be caused by the sloughed papillae.[2] The RPN of SCD contrasts with the RPN encountered in analgesic abuse, where the vasa rectae are usually spared, and peritubular capillaries are primarily involved.[36]

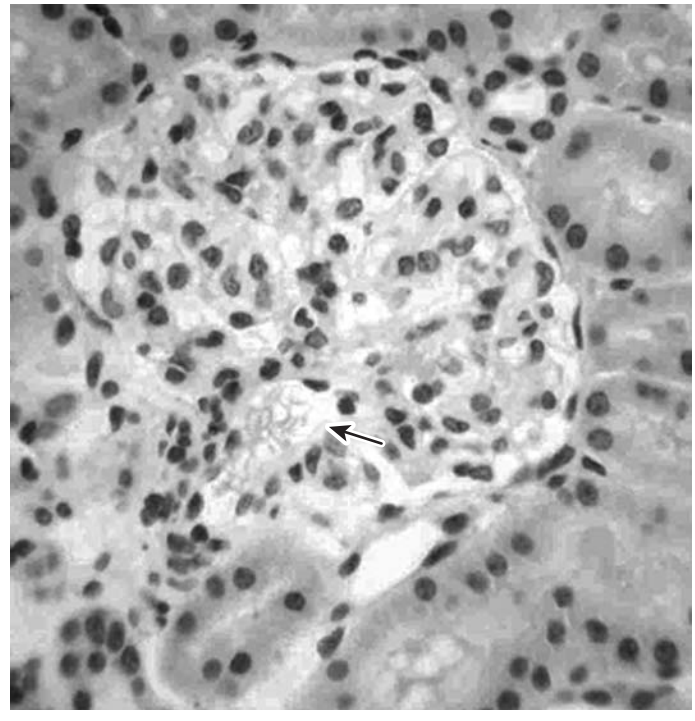

Figure 19.3 Light microscopy of renal biopsy in a child with a history of recurrent gross hematuria. The glomerulus appears morphologically normal, and sickled red cells are seen within the capillary lumens. The arrow points to the sickled cells in afferent arteriole.

Sickle glomerulopathy

The usual renal biopsy findings in chronic sickle cell glomerulopathy are glomerular hypertrophy and FSGS.[4] Eight of the 10 adult patients with Hb SS disease who underwent renal biopsy for investigation of proteinuria and renal impairment showed FSGS, involving a mean of 27% of glomeruli.[5] Global sclerosis was noted in two biopsies. Focal tubulointerstitial fibrosis adjacent to sclerotic glomeruli was common, and all of the non-sclerotic glomeruli were enlarged, with diameters of 186±14.5 μm, vs. 137.9±19.3 μm in controls. Immunofluorescence was positive only for IgM, C3, and C1q in the sclerotic segments. Electron microscopy did not demonstrate any immune electron-dense deposits. Focal electron-lucent expansion of the subendothelial zone was noted in six patients, with occasional mesangial cell interposition. No new mesangial matrix material, suggestive of the diagnosis of membranoproliferative glomerulonephritis (MPGN), was observed in these areas. The non-immune complex deposits found in glomeruli may result from iron–protein complexes.[32] MPGN-like lesions, as well as 'collapsing' and 'expansive' sclerosis, have been reported in SCD by others.[6,37] In SCD with medullary fibrosis, juxtamedullary nephrons are the most affected by FSGS.

In addition to FSGS, focal cortical infarcts are a common late finding in sickle cell nephropathy.[32] Renal medullary carcinoma, almost exclusively found in SCD, has distinctive markers, including a special hypoxia-inducible factor, distinct from collecting duct carcinoma.[34]

Clinical manifestations

Sickle cell crises are painful episodes of vaso-occlusion, often accompanied by fever without documented infection on the second or third day. Neither abnormal blood viscosity nor the number of sickle cells can predict the frequency of crises.[38] The incidence of pain crises is 0.8 episodes/year in SS and 1 episode/year in S-β-thalassemia.[39] With greater degrees of anemia, there is less pain, possibly because of diminished blood viscosity. With increasing HbF, there are proportionally fewer painful crises, suggesting a beneficial effect of even modest increases in HbF.[39] Intense abdominal pain can be a manifestation of painful sickle crisis. In contrast to 'surgical abdomen', signs of peritoneal irritation, such as rebound tenderness, are usually absent in these patients. The time course of clinical manifestations of SCD is given in Figure 19.1.

Hematuria

Painless gross hematuria is the most dramatic clinical event in SCD.[38] Gross hematuria is usually unilateral, more commonly affecting the left side, possibly due to increased venous pressure in the left renal vein.[40] Hematuria can occur at any age and is more often reported with HbAS, which has a far higher genetic prevalence than SS.[17] Both microscopic and gross hematuria can be the first manifestation of papillary necrosis, or medullary cell carcinoma.[41,42]

Priapism

Priapism is a low blood flow vaso-occlusive state affecting the penis in patients with SCD. Its incidence in male children between 5 and 20 years old has been reported to be 2–18%.[43,44] Incidence is significantly higher (38%) in adults.[45] The painful, hot, tender erection is most often encountered upon waking and can last up to several hours. Mean age at onset of priapism in children was reported by Mantadakis et al to be 12 years, and the actuarial probability of experiencing it by 20 years of age was estimated to be 89±9%.[44] Priapism may be preceded by 'stuttering', or frequent and intermittent erections for days or weeks. In children, the engorgement usually affects the corpora cavernosa, not the corpus spongiosum, and the glans is flaccid.[32] The pain is referred to the perineum and to the abdomen, requiring analgesia. Exchange transfusion is an effective treatment. Some patients may require surgical drainage or a shunt. Fibrosis in corpora cavernosa may result in impotence.[32]

Acute renal failure

Acute renal failure (ARF) occurs frequently in patients with SCD, especially those who are hospitalized. Sklar et al reported a twofold or greater increase in serum creatinine was found in 12 of 116 (10.3%) hospitalized patients with SCD.[46] Acute renal failure was most often seen in association with infections and evidence of rhabdomyolysis, and in patients with lower Hb (mean 6.4 vs 8.7 g/dl).[46] Volume depletion was the most common precipitating cause of ARF. Eighty-three percent of patients survived, with recovery of renal function in all surviving patients. Use of non-steroidal anti-inflammatory drugs (NSAIDs) may also be a causative factor in the precipitation of ARF in some patients with SCD.[47]

Rhabdomyolysis with ARF and disseminated intravascular coagulation has been reported rarely in sickle trait (SA) during rigorous exercise.[48] Physical exercise has also been reported to cause sudden death in patients with sickle cell trait.[49]

Renal papillary necrosis

RPN is usually discovered by radiologic investigation of patients with painless gross hematuria.[24] Papillary sloughing and passage of the tissue down the ureter can cause intense colicky flank or abdominal pain (clot colic), in addition to hematuria. RPN can occur in patients with sickle cell trait as well as in very young children.[40]

Hypertension

Blood pressure of SCD patients is generally lower than that in the general population.[50] Systemic hypertension occurs in 2–6% of adults with SCD, compared with the published

incidence of 28% in the adult African-American population of the United States.[7,50,51] Hypertension is commonly seen in patients when renal insufficiency is present, in addition to SCD.[52] Hypertensive crises may be precipitated in previously normotensive patients with SCD during blood transfusion.[53]

Tubular dysfunction

The most common clinically manifest tubular abnormality in SCD is a urinary concentrating defect. Typically, HbSS patients achieve a urine concentration of about 400 mOsm/kg after 8–10 hours of water deprivation, compared with about 900 mOsm/kg in controls.[21] Even patients with sickle trait can have a diminished urinary concentrating capacity.[54] Inability to concentrate urine results in an increased frequency of urination and enuresis in children with SCD, and makes them susceptible to dehydration in warm weather. The concentrating defect in SCD is not responsive to vasopressin, since vasopressin generation is normal. The concentrating defect is unique to sickling hemoglobinopathies, and concentrating defects are not seen in other anemias.[20] Urinary dilution is normal.

An incomplete distal renal tubular acidosis (RTA) may complicate SCD, but it is not usually a clinical problem.[15] The minimum urine pH achieved in response to NH_4Cl loading is not as low as in controls (5.8 vs 5.1), but total NH_4 excretion is normal. Consequently, titratable acidity is reduced.[27] Distal RTA with hyperkalemia (type IV) has also been described in SCD, with a reduced ability to lower urine pH in response to Na_2SO_4, and inadequate K^+ secretion, especially in patients with decreased renal function.[55] In one series, six of nine nephrotic SCD patients were reported to have type IV RTA.[56] Although the electrolyte abnormalities resemble those seen in type IV RTA, acidosis and hyperkalemia result from an aldosterone-independent end-organ failure due to medullary fibrosis. The intracellular shift of potassium, largely under the influence of β_2-adrenergic stimulation, is protective against the large load of potassium released from sickled cells. Therefore, the use of β-blockers, or angiotensin-converting enzyme (ACE) inhibition may result in hyperkalemia in these patients.[15]

Diuretic response is poor in SCD, because it is dependent on more distal sodium delivery. Proximal tubular phosphate reabsorption, which usually parallels sodium reabsorption, is also increased. This may cause hyperphosphatemia, especially in the presence of an increased phosphate load generated by hemolysis.[15]

In summary, the tubular dysfunction of SCD manifests a defect in urine concentration, whereas dilution is maintained. Hydrogen ion and potassium secretion functions are only mildly affected, and proximal tubular mechanisms are exaggerated.

Proteinuria

The association of significant proteinuria with SCD is well recognized, often associated with hematuria, and is discussed in the context of sickle glomerulopathy. Indeed, the sickle cell glomerulopathy is defined as nephrotic-range proteinuria in patients with SCD. Although long-term studies have not been carried out, SCD glomerulopathy appears to have a more rapid course than other causes of nephrotic syndrome. Bakir et al reported that two-thirds of proteinuric patients developed advanced CKD within 2 years.[56] The onset of renal failure is heralded by an increasingly inadequate erythropoiesis.[52]

Evaluation

Continued gross hematuria represents a form of renal 'sickle crisis' in a known HbSS or HbAS patient. Other treatable causes of hematuria, including papillary necrosis and the recently described distinctive renal medullary carcinoma in patients with sickle hemoglobin, must be excluded.[57] Moderate discomfort, often lateralizing to one side, accompanies hematuria, but severe pain is uncommon. Renal and bladder ultrasound can rule out bleeding from a stone or tumor and renal papillary necrosis. Increased echodensity of medullary pyramids on ultrasound is common in SCD.[58] A review of ultrasound studies in young SCD patients (aged 10–20 years old) found diffusely increased echogenicity in 9%, and medullary echodensity in 3%.[59] Surprisingly, echodensity was greater in the clinically milder genotypes, being 37 and 79% of SC and S-Thal patients, respectively. These findings may be indicative of subclinical nephrocalcinosis or iron deposition.

The diagnosis of RPN in SCD has been conventionally made by intravenous urography (IVU). The visualization of the renal architecture in SCD by IVU, which is now seldom performed, is probably unnecessary. Sonography and helical tomography can sometimes identify the early medullary form of papillary necrosis.[61,62] On IVU, calyceal clubbing is an early indication of RPN and was noted in 39% of patients in one study, whereas 23% had definite evidence of RPN.[60] Cortical scarring, as found in pyelonephritis, does not accompany the calyceal clubbing of SCD.[61] A 'medullary' form of RPN is more common, consisting of an irregular medullary cavity, often with sinus tracts.[10] The base of the calyx and its outline are well preserved.[61] A later finding is a distinctive calcification of the medullary pyramids in a 'garland' pattern shadowing the pelvis. The progression to a 'papillary' form of RPN results in clubbing and caliectasis (Figure 19.4b). This radiologic picture is more common in analgesic nephropathy, in which an area of sequestration is often found, resulting from infarction of a large area of the papilla.[63] The contribution of infection to the development of RPN is interesting but unclear. A prospective survey of symptomatic SCD patients found that 11 of 18 SA patients had a form of RPN, and 8 of these patients had some evidence of associated infection.[10] Asymptomatic patients can also have RPN, including patients with HbSS, HbSC, and HbS-Thal. Renal scan (Tc-99m-methylene diphosphonate) abnormalities consisting of increased uptake are commonly seen in HbSS.[64] This is probably reflective of regional stasis or tubular ischemia, causing peritubular extravasation.

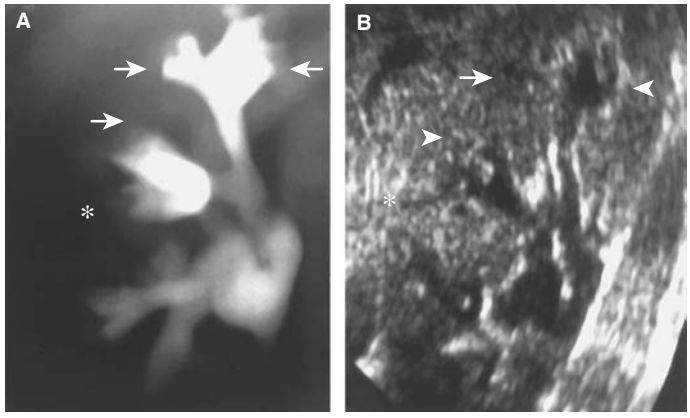

Figure 19.4 (A) Tomographic intravenous pyelography of an 18-year-old patient with abdominal pain and hematuria. Papillary necrosis is evident from blunted medullary cavities, especially the upper pole (arrows). The bases of the calyces are preserved. The middle pole calyx has a possible sinus tract (*). (B) Ultrasonographic visualization of the same kidney. The middle pole exhibits deep extensions into the papilla, probably sinus tracts, typical of the 'papillary' form of RPN. The arrows point to corresponding areas. (Reproduced with permission from Pediatric Nephrology. Barratt TM, Avner EA, Holliday MA (editors). Baltimore: Williams & Wilkins; 1999: 497.)

Hyperfiltration complicates the estimation of GFR in patients with SCD. The reliability of the techniques of GFR estimation that can substitute for C_{In} have not been validated in patients with elevated GFR. Because C_{Cr} usually exceeds C_{In} in normals, its validity in SCD is uncertain. Estimation of GFR, by formulas based on P_{Cr} alone (Schwartz's formula),[65] can lead to an even greater overestimation of GFR in SCD patients. For most clinical purposes, a precise measurement of GFR is unnecessary, but a decline in GFR by the same estimation over time, particularly when accompanied by proteinuria, is ominous.[66]

Proteinuria detected by urine dipstick in a patient with SCD should be quantified and renal function assessed. If hematuria is present, RBC casts may point to a pathology other than sickle cell glomerulopathy. Evidence of hypertension, hypocomplementemia, and antinuclear antibodies also suggests other diagnoses. Judging from the findings in our series, few other additional studies are indicated.[5] Microalbuminuria has been documented in older children with SCD, and has been proposed to be a predictor of early sickle nephropathy in children.[67,68]

Anemia in SCD may not be solely due to lack of erythropoiesis, but can be contributed to by gastrointestinal bleeding. Excess iron stores may now be assessed by biomagnetic susceptometry, but only in specialized centers.[69] MRI may provide a more quantitative measurement of iron stores.

Treatment

Hematuria

In view of the benign nature of hematuria in SCD, a conservative approach to management is appropriate.[17] High rates of urine flow should be maintained by both intake of hypotonic fluid (4 L/1.73 m^2 surface area per day) and diuretics (thiazide or a loop diuretic). This can help to minimize the possibility of developing clots in the bladder.[40] Diuresis also reduces medullary osmolarity and may therefore help alleviate sickling in the vasa rectae.

The combination of vasopressin and administration of hypotonic fluid to reduce plasma osmolality has been suggested.[17] This approach induces water uptake by RBCs in vitro, thereby reducing the effective HbS concentration and making RBCs less likely to sickle. However, it has been proven neither safe nor effective. Volume expansion by normal saline, especially when coupled with hypertransfusion, can predispose the patient to congestive heart failure and should be avoided.

Because sickling is facilitated by an acidic environment, alkalinization of the urine by administering sodium bicarbonate may reduce sickling in a urine environment, but its impact on the intrarenal medullary sickling may be less relevant.[40] Alkalinizing the patient to increase the O_2 affinity of hemoglobin is theoretically valid but not of proven clinical value.[17] Blood transfusions may be necessary for blood loss and could be helpful by increasing the proportion of normal HbAA cells, thereby reducing sickling.

Epsilon-aminocaproic acid (EACA) inhibits fibrinolysis, allowing stabilization of clots and achieving hemostasis, and may be used in severe gross hematuria. The effective dosage in an adult is 8 g/day; lower dosages may be adequate to arrest hematuria, starting with 1 g/1.73 m^2 orally three times daily and increasing the dose until hemostasis occurs.[17] Because of the risk of thrombosis, EACA should be used with caution. Nephrectomy is rarely required for uncontrolled bleeding, since arteriographic localization and local embolization of the involved segment is possible.

RPN can be prevented experimentally by either inducing diabetes insipidus or water diuresis, thereby eliminating the medullary concentration gradient.[14] Thus, the fluid administration prescribed for gross hematuria is also appropriate to prevent RPN. ACE inhibition can experimentally induce a 50% increase in papillary blood flow.[14] This may help prevent RPN, but it could aggravate hematuria acutely by increasing blood flow to the tissues affected by bleeding. New surface-active polymers may abort sickle crises, and thus possibly the acute hematuria of SCD.[70]

Tubular dysfunction

Treatment of tubular disorders in SCD is usually unnecessary if renal function is normal. The risk of dehydration caused by decreased urinary concentrating ability requires prompt treatment of conditions that can cause dehydration. Acidosis should also be avoided and treated appropriately, when present. Hyperuricemia, resulting from increased urate production, may be aggravated by diuretics (especially thiazides) that inhibit urate secretion. Severe hemolysis may exceed the patient's ability to excrete potassium, especially in the presence of renal insufficiency, ACE inhibition, or β-blockers, or can

aggravate hyperkalemia, especially in the presence of renal impairment.[15,55]

Sickle glomerulopathy

Progression of FSGS to CKD in SCD remains difficult to assess, in part because of the difficulties in quantitation of renal function described above. It is important to minimize sickling and other factors known to promote progression of FSGS in other primary diseases or in animal models. However, it is controversial whether hemodynamic alterations by themselves can alter the progression of FSGS to ESRD.[29]

High protein intake accelerates the development of FSGS in uninephrectomized rats, without necessarily causing nephron overload.[71] In children, restriction of protein intake may carry unreasonable risks.[72] Delayed growth and development is already a particular risk in the SCD patient. Therefore, we advise avoidance of a protein intake greater than the recommended dietary allowance.

Glomerular hyperperfusion and proteinuria could be mediated through increased glomerular capillary pressure, reduction of which by ACE inhibition might protect the glomerulus from FSGS. In our 2-week trial of therapeutic efficacy, 10 adult patients with mild SCD nephropathy received enalapril, 10–20 mg/day. Blood pressure, GFR (C_{In}), and effective renal plasma flow (PAH clearance) did not change significantly, whereas proteinuria diminished by 57%, rebounding after treatment withdrawal.[5] A more recent 6-month controlled trial of enalapril in 22 SCD patients with microalbuminuria showed a significant decrease of proteinuria in the treatment group, whereas it was increased in the control group.[73] Whether long-term ACE inhibitor therapy has a salutary effect in preventing renal insufficiency is unclear.

Specific treatment of CKD in the patient with SCD has been poorly explored. Patients with advanced CKD (stages III and IV) may sometimes have symptomatic anemia and require blood transfusion. In some of these patients, treatment with erythropoietin can variably restore hemoglobin concentrations to higher levels.[74] A few patients have been treated with hydroxyurea, in addition to erythropoietin, with apparent benefit.[75]

End stage renal disease (ESRD)

The US Renal Data System (USRDS) report from 1989 through 1993 described 235 of 255 573 patients with ESRD as having SCD.[76] This is less than the expected incidence of HbSS in the total population. It is possible that physicians do not offer treatment to many patients with SCD who develop ESRD. Ojo et al reviewed the transplant results in SCD and found that, in 82 patients, there was no difference in the 1-year cadaveric graft survival.[77] The multivariable adjusted 1-year risk of graft loss indicated no significant effect of SCD: relative risk (RR) = 1.39. However, the 3-year cadaveric graft survival tended to be lower in the SCD group (48% vs 60%, $p = 0.055$) and the adjusted 3-year risk of graft loss was significantly greater (RR = 1.60, $p = 0.003$). There was a trend towards improved patient survival in the SCD transplant recipients compared with their dialysis-treated, wait-listed counterparts (RR = 0.14). In comparison with the other causes of ESRD (RR = 1.00), the adjusted mortality risk in the SCD group was higher, both at 1 year (RR = 2.95) and at 3 years (RR = 2.82) after renal transplantation. They also found a trend toward better patient survival with renal transplantation relative to dialysis in end-stage sickle cell nephropathy.[77] In another analysis of USRDS data, outcome of first transplants in 54 patients showed patient survival for SCD was 90% at 1 year and (of 30 patients) 75% at 3 years.[78] First graft survival for SCD was 82.5% at 1 year and 54% at 3 years. The proportional risk ratio for graft survival was 1.77, but after correction for patient deaths with functioning graft, it was only 1.06.

We explored the USRDS data files 2000 for evidence of the effect of SCD on the outcome of CKD.[79] Whereas the diagnostic code (assigned at the time of renal failure) for sickle cell nephropathy yielded 904 patients, further exploration of patients discovered by hospitalization codes yielded a total of 1656 patients with HbSS. Of these, 237 patients had been transplanted and 1419 were not transplanted. SCD patients were compared with all other African-American (AA) patients with ESRD; projected 10-year survival was poor for both groups, being 25% for AA and 15% for SCD. In addition, the transplanted AA patients had statistically better survival than the SCD patients, but the projected life-table survival was comparable in the two groups, being approximately 50% at 15 years. Using an age-adjusted cohort of AA patients as controls, the difference statistically disappeared ($p < 0.19$). Comparing the non-transplanted AA patients with the SCD patients yielded differences, but survival was extremely poor for both groups, being 25% for the AA patients and 14% for SCD patients at 10 years.

A comparison of the 153 transplanted SCD patients with those who were not transplanted showed a far better survival curve for the transplant recipients: 56% vs 14% at 10 years.[79] Of the 951 SCD patients with CKD discovered in the cyclosporin era (since 1991), only 53 SCD patients received renal transplants vs 898 who were not transplanted. Projected survival of the transplanted group is 67% at 7 years vs 83% for the AA cohort.

These results strongly suggest that transplantation is a better option for the SCD patient with ESRD. However, outcome is less satisfactory in comparison with other AA patients, and grafts can be lost due to demonstrable massive sickling events. Increased blood viscosity associated with a rapidly rising hematocrit can aggravate these recurrent sickle crises. Partial exchange transfusions have been used to treat these crises.[80] In one early series, seven of eight patients had frequent sickle crises after transplantation.[81] Renal venous thrombosis and infarction have also been reported.[82] In one patient with HbAS, the transplanted kidney was unfortunately removed for an apparently irreversible acute rejection, which was later demonstrated to be intrarenal sickling.[81]

During the transplantation surgery in SCD, efforts should be made to prevent the potential perioperative problems of sickling. The transplanted kidney should be warmed with saline at

37°C, dopamine infused at 4 μg/kg/min during and immediately postoperatively, and 40% oxygen provided, with intravenous fluids to decrease viscosity. Partial exchange transfusion may be provided at 4-week intervals.[81] Before an adequate erythropoietin (EPO) response is generated by the transplanted kidney, recombinant EPO should be given.

Sickle cell nephropathy has been reported to recur in the transplanted kidney after as few as 3.5 years, although other factors contributed.[83] The only agent able to significantly decrease sickling by myelosuppression of HbSS cells, thus increasing HbF, is hydroxyurea. Hydroxyurea is a cytotoxic agent that inhibits growth of erythroid burst-forming units (BFU-E).[84] In SCD, it is the SS cells that are suppressed, allowing an increase in HbF. Trials of hydroxyurea in adults and children have shown a reduction in acute crises, and allowed normal growth and development.[85,86]

Bone marrow transplantation can cure SCD, and the possibility of its being coupled with other solid organ transplants will undoubtedly be explored. Animal experiments have shown the promise of genetic transduction of an anti-sickling hemoglobin to cure sickling in mice.[87] More work is needed in this therapeutic direction.

Concluding remarks

SCD is a multi-organ disorder that can affect the kidney and lead to CKD and ESRD. Prevention of sickling is, perhaps, the most important tool in preventing the renal consequences of SCD. Developments in transplantation of these patients have advanced slowly, yet transplantation offers better survival options for patients reaching ESRD. Further work in prevention and treatment of sickle glomerulopathy is necessary in order to prevent progression to ESRD.

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Part IV

Diseases of tubular transport

20 Renal tubular acidosis

John W Foreman

In renal tubular acidosis (RTA), defective renal tubular functions lead to metabolic acidosis despite normal acid production from metabolism and dietary intake. RTA is characterized by hyperchloremic metabolic acidosis. It can occur sporadically or as a heritable disorder, either as an autosomal dominant or recessive trait, or may present as part of a more generalized tubular disorder, such as the Fanconi syndrome. RTA classically has been defined as involving either the proximal (type II) or distal (type I, IV) portion of the nephron. In the past, the urine pH has been the central diagnostic tool in the work-up of a patient suspected of having RTA. Halperin and his group have challenged this concept and have suggested that the rate of ammonium secretion may be the most important diagnostic index.[1] They further suggest that identification of the abnormal components of net acid secretion in RTA will allow a better understanding of the physiology than the earlier classification system.

Maintenance of acid–base balance

The typical US diet generates approximately 1 mEq/kg/day of H^+ in an adult, and 1–3 mEq/kg/day in children and infants. Infants and young children generate more acid per day than adults, in part because the formation of bone consumes the buffers, hydroxyl ion (OH^-) and phosphate, in order to make hydroxyapatite. Most of the acid generated by metabolism is buffered by bicarbonate (HCO_3^-) to form carbonic acid (H_2CO_3), which is converted to water (H_2O) and carbon dioxide (CO_2) by erythrocyte carbonic anhydrase (CA). The acid is thus eliminated from the body by the lungs. However, to continue to accomplish this respiratory management of the acid–base balance, the kidney must generate an equivalent amount of HCO_3^-. In addition, however, some acids cannot be 'blown off' in this manner, and are excreted by the kidney. This acid secretion by the renal tubule is composed of 'titratable acid' (TA), mainly in the form of monobasic phosphate ($H_2PO_4^-$) and ammonium ion (NH_4^+). However, any HCO_3^- or, in situations of abnormal metabolism, organic anions, which are potential sources of HCO_3^- when completely metabolized, that are lost in the urine diminish the net acid excreted (NAE) by the kidney. This relationship can be shown as:

$$NAE = TA + N\,H_4^+ - HCO_3^- - \text{metabolizable anions} \quad (1)$$

When the urine pH is less than 6.5, there is little to no HCO_3^-. Although many of these organic anions are difficult to measure directly, their presence can be suspected if there is a significant difference (greater than 100 mOsm/L) between the measured urine osmolality (U_{osm}) and the calculated osmolality from:

$$\text{Calculated } U_{osm} = 2 \times U_{Na} + 2 \times U_K + U_{Urea}/2.8 + U_{Glucose}/18 \quad (2)$$

In order to maintain body pH, the kidney must regenerate HCO_3^-. This is done by combining CO_2 with H_2O to form H^+ and HCO_3^- in renal tubule cells, a process catalyzed by CA. The newly generated HCO_3^- is transported into the blood, replacing the lost HCO_3^-. The H^+ is eliminated in the urine, titrated to phosphate as monobasic phosphate ($H_2PO_4^-$) and as ammonium (NH_4^+). The urinary concentration of phosphate, generally varies only over a small range. However, NH_4^+ generation and excretion can increase by several-fold, especially under conditions of excess acid production. Thus, the major response to acidosis by the kidney is increased NH_4^+ production and elimination.

Renal handling of bicarbonate

In a normal adult, approximately 4500 mEq/day of bicarbonate must be reclaimed from the glomerular filtrate (180 L/day glomerular filtrate × 25 mEq/L plasma bicarbonate concentration = 4500 mEq). Proximal tubular bicarbonate reabsorption is accomplished by the secretion of H^+ into the tubular lumen, in exchange for Na^+, via the luminal membrane sodium/hydrogen exchanger (NHE3) (Figure 20.1). The driving force for this exchange is the Na/K-ATPase on the basolateral membrane,

where 3 Na^+ ions are transported out of the cell in exchange for 2 K^+ ions, leading to an electrochemical (low intracellular Na^+ concentration and negative potential charge relative to the lumen) gradient favoring Na^+ entry into the cell. A small amount of H^+ is pumped from the tubular cell into the lumen via a H^+-ATPase pump. The hydrogen for this process is generated in the cytosol by reaction of CO_2 and H_2O, catalyzed by carbonic anhydrase II (CAII). The HCO_3^- generated in this process exits the cell via the Na^+, HCO_3^- exchanger (NBC1) that is coded for by the gene SLC 4A4.

The hydrogen ion transported into the proximal tubule lumen combines with the filtered bicarbonate to form carbonic acid and, subsequently, CO_2, a reaction rapidly catalyzed by carbonic anhydrase IV (CAIV), which resides on the apical and basolateral membrane of the proximal tubule and thick ascending limb of the loop of Henle (TAL). Approximately 80–90% of the filtered load of bicarbonate is reabsorbed in the proximal tubule. Factors increasing HCO_3^- reabsorption include increased filtered load, low peritubular pH and high PCO_2, angiotensin II, extracellular volume contraction, and potassium depletion. Acute administration of parathyroid hormone decreases proximal HCO_3^- absorption.

The TAL reabsorbs the majority of HCO_3^- leaving the proximal tubule (Figure 20.2). Apical Na^+/H^+ exchange mediates most of H^+ secreted in the lumen. The HCO_3^- generated in the cell can exit via several transporters, including Na^+/HCO_3^- and K^+/HCO_3^- cotransporters and the Cl^-/HCO_3^- exchanger. The distal nephron is responsible for reabsorption of the rest of the filtered HCO_3^-, where H^+ is actively pumped into the lumen via the H^+-ATPase pump and H^+/K^+-ATPase pump. Bicarbonate exits the cell via the Cl^-/HCO_3^- exchanger (AE1).

Distal tubular acidification

The distal nephron consists functionally of three segments:

- the cortical collecting tubule (CCT)
- the outer medullary collecting tubule (OMCT)
- the inner medullary collecting tubule (IMCT).

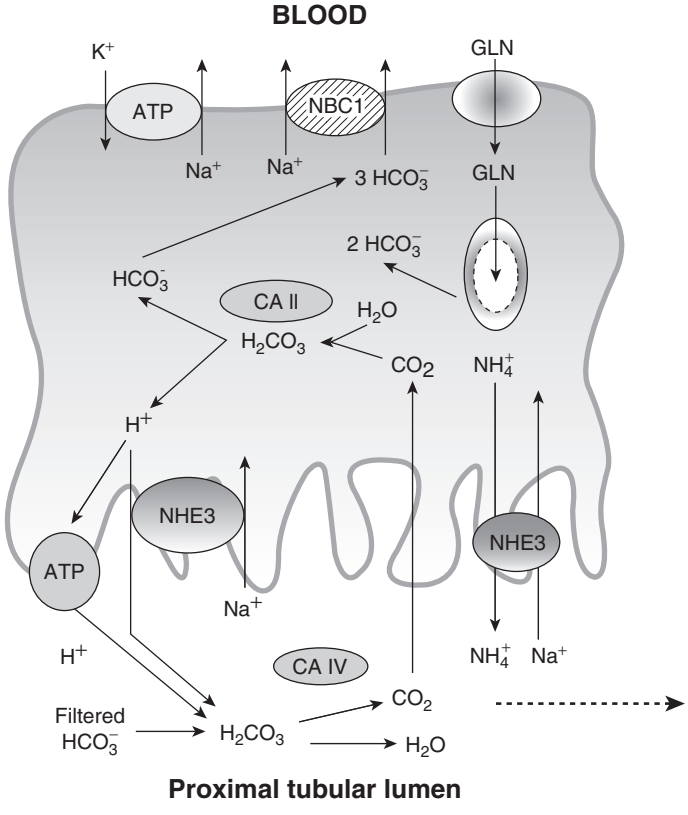

Figure 20.1 Acid–base transport by the proximal tubule. H^+ generated by CAII exits the cell and into the lumen via the Na^+/H^+ exchanger 3 (NHE3) and the H^+-ATPase. There it combines with filtered HCO_3^- to form CO_2 (facilitated by CAIV), which diffuses back into the cell. HCO_3^- exits the cell and into the blood via the Na^+-HCO_3^- cotransporter (NBC1). Glutamine (GLN) enters the cell via a specific transporter, where it is metabolized to 2 HCO_3^- and 2 NH_4^+ molecules. NH_4^+ exits the cell via the Na^+/H^+ exchanger 3 in place of H^+.

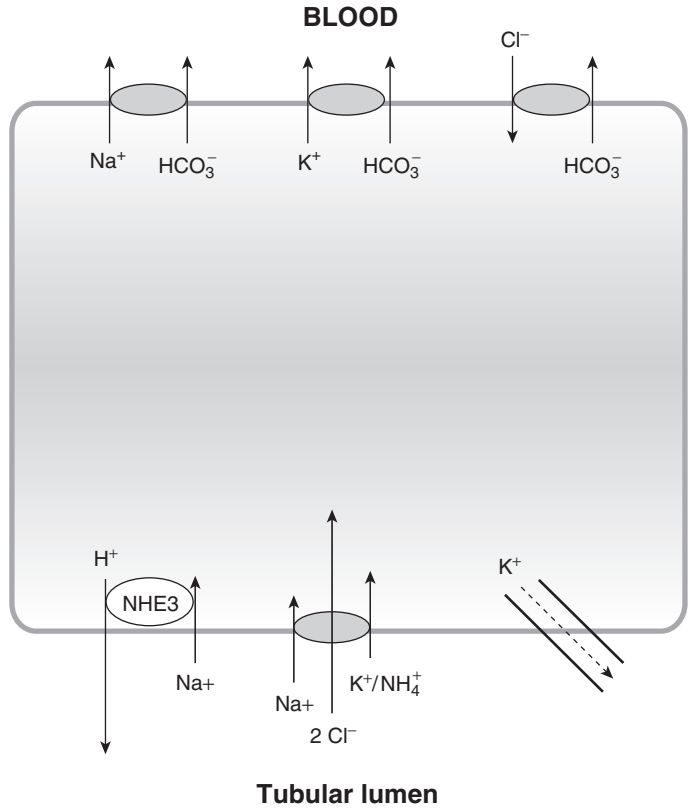

Figure 20.2 Acid–base transport by the thick ascending limb (TAL) of the loop of Henle. The remaining filtered HCO_3^- is reabsorbed by combining with H^+ secreted by the Na^+/H^+ exchanger 3 (NHE3). HCO_3^- exits the cell via several transporters, including Na^+/HCO_3^- cotransporter, K^+/HCO_3^- cotransporter, and the Cl^-/HCO_3^- exchanger. NH_4^+ can enter the cell in place of K^+ on the $2Cl^-/Na^+/K^+$ transporter for recycling in the medullary interstitium.

The CCT is a low-capacity segment in which acidification is regulated by Na^+ transport that generates a lumen negative membrane potential. The OMCT has a high capacity for H^+ secretion but does not transport Na^+. The IMCD has a low capacity for H^+ secretion and is regulated by systemic acid–base status and K^+ balances both in terms of net H^+ secretion and NH_4^+ transport. The cell responsible for H^+ secretion is the α-intercalated cell in the collecting duct. Most H^+ secretion occurs via the H^+-ATPase pump, with some by the H^+/K^+-ATPase pump (Figure 20.3). Bicarbonate exits the cell via the basolateral anion exchanger (AE1).

Mineralocorticoids play an important role in H^+ secretion, both by Na^+-dependent and Na^+-independent mechanisms. Mineralocorticoids in the CCT increase Na^+ absorption, increasing lumen negativity and favoring H^+ secretion. Mineralocorticoids also directly stimulate H^+ secretion in the OMCT and the IMCT. Low systemic pH and high PCO_2 augment H^+ secretion in the distal nephron.

Ammonia production and excretion

Excreted H^+ must be buffered to prevent extreme luminal acidity. Ammonia serves as an important buffer system in this location (Figure 20.4). Ammonia (NH_3) is highly permeable to cell membranes. Secreted H^+ converts luminal NH_3 to NH_4^+, thus lowering the concentration of NH_3, allowing more NH_3 to diffuse into the lumen. Trapped NH_4^+ is relatively impermeant to cell membranes. The higher H^+ ion concentration in the lumen of the distal nephron compared with the medullary interstitium further favors the transfer of NH_3 into the distal nephron lumen.

Most ammonia is generated in the proximal tubule cell by amino acid metabolism, principally glutamine. The rate-limiting steps in glutamine metabolism are glutaminase and phosphoenolpyruvate carboxykinase (PEPCK). The end products of glutamine metabolism are two NH_4^+ ions and α-ketoglutarate (α-KG). Further metabolism of α-KG yields two 'new' HCO_3^- ions, which are transported out of the cell across the basolateral membrane to restore those lost in the extracellular fluid (ECF) by buffering acid products of metabolism. However, NH_4^+ must be eliminated from the body. If NH_4^+ enters the bloodstream, it will be transported to the liver, where it is combined with 2 HCO_3^- ions to form urea, leading to no net addition of HCO_3^- to the body. To accomplish this, NH_4^+ is preferentially secreted across the apical membrane by the Na^+/H^+ antiporter. In the proximal straight tubule, the low luminal pH compared with that of the cell allows NH_3 diffusion

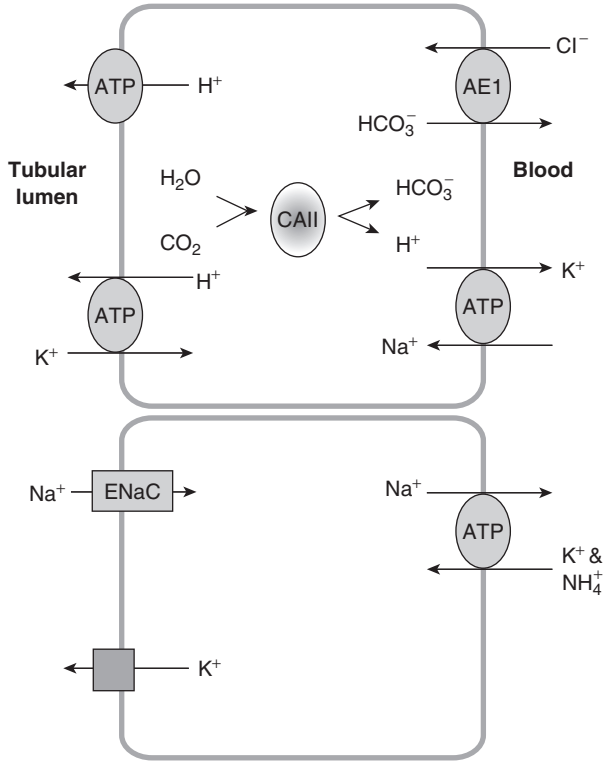

Figure 20.3 Acid–base secretion in the distal nephron. H^+ is generated from CO_2 by carbonic anhydrase II (CAII) in the α-intercalated cell and exits via the H^+-ATPase or the H^+/K^+ exchanger. HCO_3^- exits the cell via the AE1 Cl^-/HCO_3^- exchanger. NH_4^+ can enter the cell from the interstitium by competing with K^+ on the Na^+/K^+-ATPase. Na^+ enters the cell via the sodium channel (ENaC), generating a lumen to cell negative gradient.

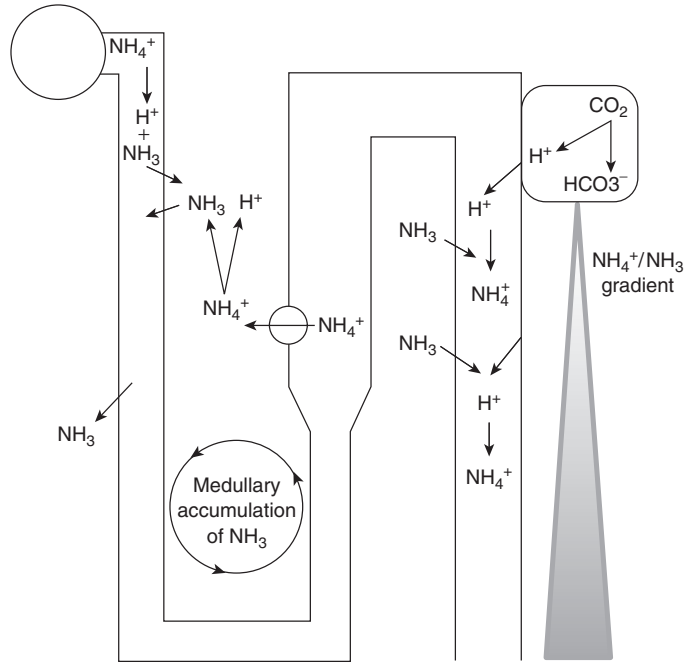

Figure 20.4 Renal ammonia metabolism. NH_4^+ is generated from glutamine in the proximal tubule cell. As the tubular fluid travels down the thin limb of the loop, water abstraction concentrates the luminal HCO_3^-, increasing the luminal pH favoring NH_3. The NH_3 diffuses out of the lumen and into the medullary interstitium. The $2Cl^-/Na^+/K^+$ transporter can also actively transport NH_4^+ out of the lumen. Both of these processes lead to NH_4^+/NH_3 accumulation in the medulla and an increasing concentration, favoring ammonia entry into the medullary collecting duct.

and NH_4^+ trapping. Acidosis stimulates glutamine release from muscles, uptake by the proximal tubule cells, and metabolism to NH_4^+. Acidosis also increases glucocorticoid levels, which in turn stimulates ammoniagenesis. Hypokalemia also stimulates ammoniagenesis and hyperkalemia inhibits it. Angiotensin II increases ammoniagenesis and proximal tubule secretion of NH_4^+.

As fluid leaves the proximal tubule, a number of processes lead to high medullary ammonia–ammonium concentrations. With the abstraction of H_2O from the thin descending limb of the loop of Henle, the tubular fluid is alkalinized by concentrating luminal HCO_3^-, favoring NH_3 efflux into the interstitium. In the TAL, NH_4^+ is actively transported into the cell by the $Na^+/2Cl^-/K^+$ cotransporter by substituting for K^+. The negative charge in the lumen facilitates NH_4^+ movement into the interstitium. Approximately one-third of the NH_4^+ transported in the TAL is by a paracellular route. Thus, this arrangement of transporters in the loop of Henle and the slow flow in the vasa recta leads to a marked concentration gradient in the medulla, mirroring that for urea.

The high interstitial NH_3 concentration facilitates its diffusion into the collecting duct, especially the ICMT, where it is 'trapped' by the secretion of H^+ to form NH_4^+. NH_4^+ can also enter the collecting tubule lumen by substituting for K^+ on the Na^+/K^+-ATPase. This interaction of K^+ and NH_4^+ on the $Na^+/2Cl^-/K^+$ cotransporter and Na^+/K^+-ATPase is another mechanism by which plasma K^+ regulates NH_4^+ excretion. The net excretion of NH_4^+, and thus acid excretion, is dependent on the formation in and transport out into the proximal tubule lumen, the development of the high interstitial medullary gradient, and the trapping in the collecting duct by H^+ secretion.

Clinical spectrum of renal tubular acidosis

The signs and symptoms of RTA are often quite protean and non-specific, such as anorexia, vomiting, constipation, polyuria, and polydipsia. Failure to thrive is a usual finding in young children. Hyperchloremic metabolic acidosis (HCMA), or normal anion gap acidosis (normal anion gap is between 8 and 16 mEq/L), is evident in virtually all untreated patients with RTA. Nephrocalcinosis, nephrolithiasis, and musculoskeletal complaints are the most common presentation of classic RTA in older children and adults. Patients with RTA, especially classic distal RTA (DRTA), may present with life-threatening acidosis and hypokalemia. Rickets may be seen in classic DRTA but is more common in patients with Fanconi syndrome. RTA may be seen in the context of other organ dysfunctions, such as nerve deafness or osteopetrosis. Volume contraction and HCMA are also seen in infants with true- or pseudohypoaldosteronism. RTA is seen in adults with aldosterone deficiency and hyporeninemia from diabetes mellitus with renal insufficiency, or a variety of interstitial diseases.

Clinical tools for evaluation

Anion gap

The first step in evaluating a patient for RTA is to look for HCMA by determining the anion gap (AG) in the serum of patients with acidosis (Figure 20.5).

$$Na^+ - (HCO_3^- + Cl^-) = AG \quad (3)$$

An AG between 8 and 16 is normal; AG > 16 is elevated.

The serum HCO_3^- should be measured soon after obtaining the serum. Factors which can lead to a falsely low HCO_3^- concentration include:

- allowing the sample to remain in contact with red cells for a prolonged period of time
- obtaining the blood by 'heel prick'
- prolonged tourniquet time.

Urine pH

Measuring the urine pH is the traditional method for evaluating patients with RTA. While urine pH is useful, its utility lies in helping to dissect the locus of the defect in a patient with RTA rather than making the diagnosis, as pointed out by Carlisle et al.[1] The urine pH varies quite widely normally, depending on diet. Furthermore, patients with chronic acidosis and normal renal tubular function will have a urine pH between 5.4 and 6.4.[2,3] Urine pH should be measured by glass electrode, as urine dipsticks are relatively inaccurate.

Urine anion gap

As mentioned previously, urinary ammonium excretion is the prime renal defense against an acid load. Therefore, determining the rate of urine NH_4^+ excretion is the next critical step in deciding whether or not there is a renal tubular acidification defect. Direct measurements of urine ammonium are not usually available to the clinician. Halperin et al[4] have shown that an estimate of urine ammonium can be made by determining the urine net charge or anion gap. The urine cations, Na^+, K^+, NH_4^+, Ca^{2+} and Mg^{2+}, must balance the urine anions, which are Cl^-, HCO_3^-, PO_4^-, SO_4^-, and organic anions. Urine Ca^{2+}, Mg^{2+}, PO_4^-, and SO_4^- are usually in relatively low and fixed concentrations such that they can be ignored. If the urine pH is below 6.5, then the urine HCO_3^- concentration will be very low. Unless there is a disorder of metabolism, urine organic anion concentrations will also be very low. Therefore, under most circumstances, the major ions in urine are Na^+, K^+, NH_4^+, and Cl^-. Of these, Na^+, K^+ and Cl^- can be easily measured.

$$Na^+ + K^+ - Cl^- = \text{urine anion gap or urine net charge} \quad (4)$$

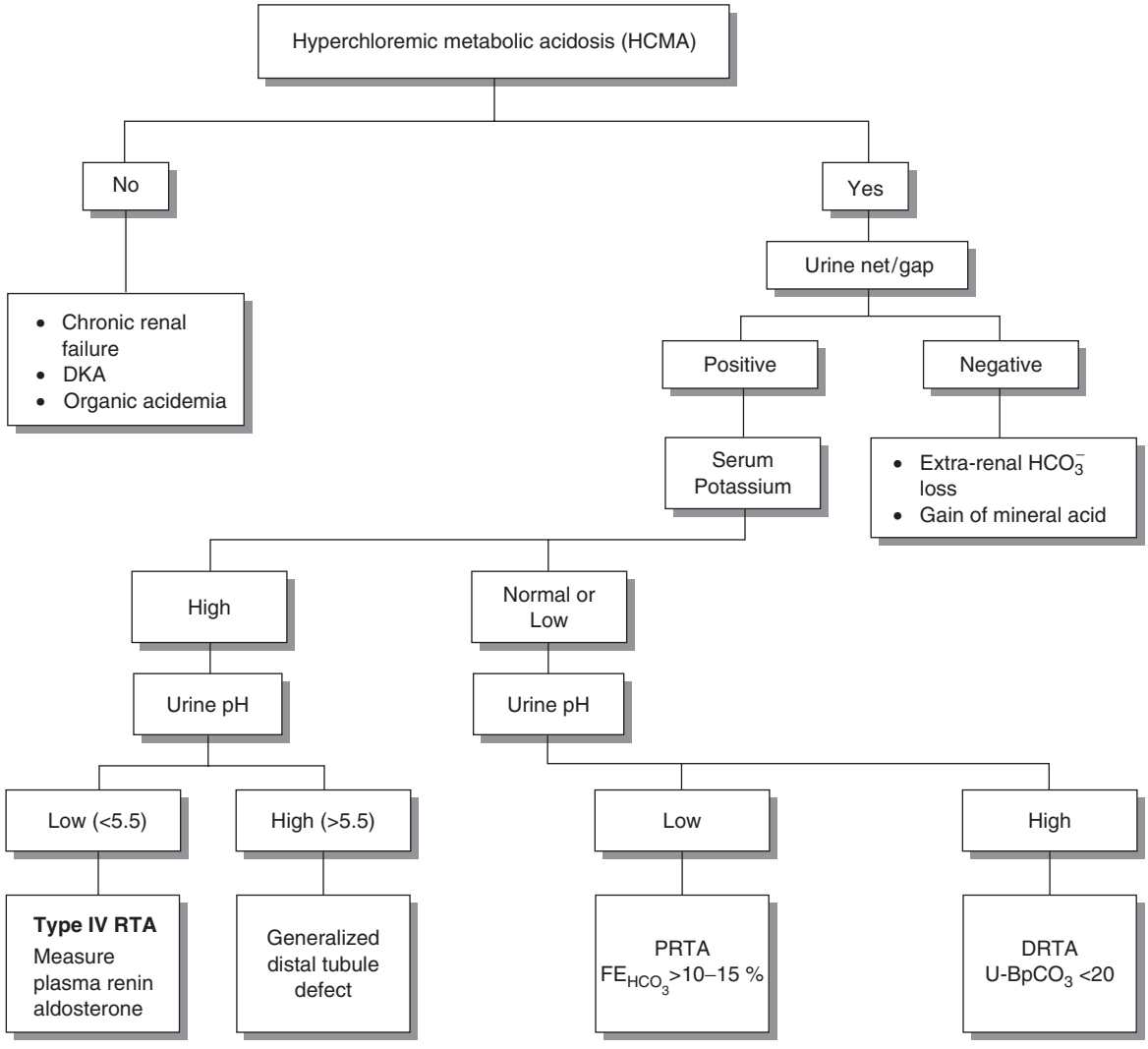

Figure 20.5 Work-up of child with suspected RTA. DKA, diabetic ketoacidosis.

Interpretation

Most instances of increased metabolic acid production are associated with a raised anion gap, but occasionally a patient presents with HCMA and a positive urine net charge (suggestive of low NH_4^+) yet has increased metabolic acid production and increased urine NH_4^+ rather than RTA. Examples of this result from glue-sniffing (toluene ingestion) and, rarely, diabetic ketoacidosis (DKA). The positive urine net charge occurs because a large amount of the urinary NH_4^+ is excreted with the organic anion of the metabolic acid rather than chloride. If this is suspected, the difference between the calculated urine osmolality (Eqn 2) and the measured osmolality can be used to detect the presence of significant quantities of unmeasured anions and as an estimate of NH_4^+ excretion. This difference should be less than 100 mOsm/kg water. If the difference is more than 100 mOsm/kg water, then it is likely there is a significant concentration of an organic anion, such as β-hydroxybutyrate in DKA or hippurate in glue-sniffing. One half of this difference can be used as an estimate of the ammonia concentration.

Fractional excretion of bicarbonate

To test the tubular ability to reclaim the filtered load of HCO_3^-, the fractional excretion (FE) of HCO_3^- can be determined after the serum HCO_3^- has been restored to normal (22–25 mmol/L) by simultaneously measuring the serum (S) creatinine and HCO_3^- and the urine (U) creatinine and HCO_3^-:

$$FE_{HCO_3^-} = \frac{U_{HCO_3^-}/S_{HCO_3^-}}{U_{creatinine}/S_{creatinine}} \times 100\% \quad (5)$$

Normally this value should be <5%. With proximal RTA, the FE HCO_3^- will exceed 15%. Urine HCO_3^- is calculated by

measuring the urine pH and PCO_2 on a standard blood gas analyzer. Bicarbonate is calculated from the Henderson–Hasselbalch equation as follows:

$$HCO_3^- = 10^{(pH-pK)} \times 0.03 \times PCO_2 \quad (6)$$

Although the pK in urine is not constant, one can assume the pK is close to 6.1.

Urine–blood PCO_2

The urine PCO_2 concentration in alkaline urine has been used to test the distal nephron's ability to secrete H^+.[4] By testing under alkaline conditions, the tubule won't have to secrete hydrogen ions against a gradient. In the distal tubular lumen, the H^+ combines with HCO_3^- and the resulting H_2CO_3 only slowly decomposes into H_2O and CO_2, since CA is not present on the luminal membrane as it is in the proximal tubule. This slow decomposition means that CO_2 is formed in the lower urinary tract where the volume to surface area favors slow dissipation of the CO_2 gradient. The countercurrent system in the medulla also maintains a high urine PCO_2. To perform the test, the urine pH and HCO_3^- concentration are raised to > 7.5 and 85 mmol/L by infusing HCO_3^- or administering acetazolamide, 17 mg/kg, and the PCO_2 is measured.[5] A normal response is urine PCO_2 that exceeds the blood PCO_2 by 30 mmHg. If this difference is less than 30 mmHg, then distal hydrogen ion pumping is defective and is suggestive of DRTA. Patients with proximal renal tubular acidosis (PRTA) will have a urine PCO_2 that exceeds the blood PCO_2 by 30 mmHg.

Acid loading

The classic test for renal tubular acidosis is to determine the net acid excretion (Eqn 1) during spontaneous acidosis, or after acid loading. Most children with untreated RTA have metabolic acidosis, making acid loading unnecessary. Acid loading can be useful in equivocal cases. Traditionally, ammonium chloride (NH_4Cl) is given orally in a dose of 150–300 mg/kg.[6,7] The urine is then collected for 4–8 hours and the urine pH, titratable acid (defined as the amount of NaOH needed to raise the urine pH to 7.4) and urine ammonium are measured. Oral $CaCl_2$ (2 mg/kg) and intravenous (IV) arginine hydrochloride (150 mEq H^+/m^2 or 300 ml/m^2 of a 10% arginine solution) have also been used for acid loading.[8,9] A normal response is a lowering of urine pH to less than 5.2 and an increase of TA to above 33 μEq/min/1.73 m^2, and ammonium to above 46 μEq/min/ 1.73 m^2 (Figure 20.6).

Furosemide and sodium sulfate challenge test

A simple way of testing the distal tubule's ability to acidify the urine is to give 1–2 mg/kg of furosemide orally or intravenously. Furosemide causes an increase in distal Na^+ and Cl^- delivery. The Na^+ is reabsorbed but the poorly reabsorbed Cl^- causes a lumen-negative transepithelial potential difference and increased H^+ secretion.[10] The expected normal response is a fall in urine pH to below 5.5 and a doubling of the urinary excretion of net acid and potassium 2–5 hours after administration.

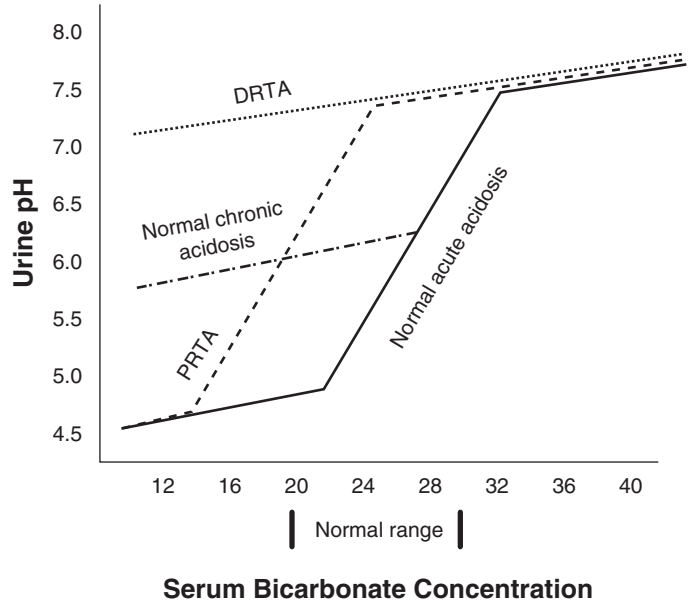

Figure 20.6 Idealized curves of urine pH vs serum bicarbonate during acidosis. The solid line represents normal children during acute acid loading. The dashed and dotted line represents urine pH after chronic acidosis in normals. The dotted line represents patients with DRTA (distal renal tubular acidosis) and the dashed line represents patients with PRTA (proximal renal tubular acidosis).

A sodium sulfate infusion (0.25–0.5 g/kg) can be also used to assess distal H^+ secretion. Sulfate is poorly reabsorbed in the distal nephron, increasing the lumen-negative transepithelial potential difference. This facilitates H^+ secretion and a fall in urine pH to below 5.2. Pretreatment with fludrocortisone augments the response to sodium sulfate.[11] However, sodium sulfate solutions are not commercially available and the test is rarely performed. An abnormal response to either sodium sulfate or furosemide suggests either a secretory (hydrogen pump) or voltage-dependent defect.

Proximal renal tubular acidosis

PRTA, or type 2 RTA usually presents with clinical features of growth failure in infants and children.[12] Recurrent vomiting is another frequent symptom. Common causes of PRTA are listed in Table 20.1. Patients with PRTA may also have generalized proximal tubular dysfunction (Fanconi syndrome) as a result of an inherited error of metabolism, such as cystinosis, tyrosinemia, galactosemia, Wilson disease, Lowe syndrome, or mitochondrial myopathies (Table 20.2). PRTA can also result from nephrotoxic proximal tubular injury, such as with use of lead, cadmium, outdated tetracycline, or ifosfamide.[13] Transient and persistent isolated PRTA has also been described.[14,15] PRTA

Table 20.1 Proximal renal tubular acidosis (defective bicarbonate reclamation)

Sporadic:
- Transient (infants)
- Cyanotic heart disease
- Renal vascular accident

Genetic:
- Autosomal dominant
- Autosomal recessive with mental retardation and ocular disease (NBC1 deficiency)
- Leigh's syndrome
- Metachromatic leukodystrophy

Carbonic anhydrase inhibition:
- Topiramate (Topamax)
- Acetazolamide
- Sulfanilamide
- Mafenide

Table 20.2 Causes of Fanconi syndrome

Inherited causes	Acquired causes
Cystinosis	Heavy metal poisoning: lead, cadmium
Hereditary fructose intolerance	Drugs: cisplatin, ifosfamide, gentamicin, azathioprine, valproic acid (sodium valproate), suramin, streptozocin, ranitidine
Tyrosinemia	
Wilson disease	Other poisonings: glue sniffing, diachrome, Chinese herbal medicine
Lowe syndrome	
Glycogenosis	Dysproteinemias: multiple myeloma, Sjögren syndrome, light-chain proteinuria, amyloidosis
Dent disease	
Mitochondrial cytopathies	Other: neprotic syndrome, renal transplantation, mesenchymal tumors
Idiopathic	

has been seen in infants with cyanotic heart disease and renal vascular accidents.

Inherited forms of PRTA

A few families have been reported with an autosomal dominant form of PRTA that presents early in life (see Table 20.1).[16] An autosomal recessive PRTA has also been described in several families in association with mental retardation and ocular abnormalities, and is caused by a defect in NBC1.[17–19] The SLC4A4 gene for NBC1 is located on chromosome 4.

Patients with osteopetrosis and CAII deficiency have both PRTA and DRTA, since CAII is important for both bicarbonate reabsorption as well as hydrogen ion secretion.[20] These patients may also have brain ventricular fluid and/or cerebrospinal fluid (CSF) abnormalities since CAII plays a role in CSF turnover in the lateral ventricles. PRTA has been described in patients with Leigh's syndrome and metachromatic leukodystophy.[21,22] Acetazolamide and anticonvulsants with acetazolamide effects, such as topiramate, lead to PRTA by inhibiting luminal CAIV (see Table 20.1).[23,24]

Pathophysiology of PRTA

The pathophysiology of PRTA, except in CAII and NBC1 deficiency, is unknown. In the rare autosomal recessive form of PRTA, the basolateral NBC1 exchanger is deficient.[19] This exchanger is necessary for transporting HCO_3^- out of the proximal tubule cell in exchange for Cl^-, and impaired activity inhibits luminal reabsorption of filtered HCO_3^-. NBC1 is also highly expressed in corneal endothelium and defective function there leads to corneal opacities, cataracts, and glaucoma.[25]

In CAII deficiency, cytosolic carbonic anhydrase (CAII) is defective and unable to generate adequate H^+ and HCO_3^- for transepithelial transport of the filtered HCO_3^-.[20] CAII is also present in the α-intercalated cell in the CCT, leading to impaired generation of H^+ for transport into the distal nephron, and leading to DRTA as well. Other possible mechanisms for PRTA include an abnormality in the Na^+/H^+ exchanger on the lumen membrane or CAIV on the luminal membrane. An abnormality at either of these sites would impair reclamation of the filtered bicarbonate, causing excessive amounts of HCO_3^- to escape the proximal tubule. This excess HCO_3^- would overwhelm the limited capacity of the distal nephron, which is able to reclaim only up to 15% of the filtered load, leading to bicarbonaturia along with the loss of Na^+ and K^+. The bicarbonaturia leads to a fall in plasma HCO_3^- and thus a fall in the filtered load. At some point, the filtered load decreases to the extent that the nephron is able to reclaim virtually the entire filtered load. The serum HCO_3^- concentration at which this occurs is termed the renal threshold for bicarbonate. At this point, the distal nephron is now able to acidify the urine.

Clinical manifestations

Patients with PRTA have a low serum HCO_3^- level, mild hypokalemia, and a urine pH below 5.5. Aldosterone and renin levels are elevated because of the renal sodium and associated water loss. The hypokalemia results from potassium secretion by the principal cells in the CCT due to elevated aldosterone levels. Polyuria is common and is the result of solute diuresis. The acidosis causes vomiting and decreased appetite and calorie intake, eventually leading to failure to thrive that is reversed with correction of the acidosis. Isolated PRTA is not associated with abnormalities of serum calcium, phosphorus, or vitamin D.

Nephrolithiasis and nephrocalcinosis are absent in PRTA, as citrate excretion is increased.

PRTA may be associated with a more global disorder of proximal tubule function known as the Fanconi syndrome. The Fanconi syndrome is characterized by glycosuria, aminoaciduria, and phosphaturia, in addition to bicarbonaturia.[13] A number of inborn errors of metabolism are associated with Fanconi syndrome, including cystinosis, tyrosinemia, hereditary fructose intolerance, Wilson disease, galactosemia, and Lowe syndrome (Table 20.2). Fanconi syndrome can be seen in acquired disorders such as heavy metal poisoning and chemotherapy (e.g. with ifosfamide and cisplatin). Rickets and osteomalacia are common in Fanconi syndrome as a result of renal phosphate losses and abnormal vitamin D metabolism.

Treatment of PRTA

The goal of PRTA treatment is the normalization of serum HCO_3^-. However, as serum HCO_3^- increases, urinary HCO_3^- losses increase. Thus, anywhere from 2 to 20 mmol/kg/day of alkali supplementation, either as bicarbonate or as an anion that can be metabolized to form bicarbonate, are necessary for correction of metabolic acidosis in PRTA (Table 20.3). Given that the ability of the nephron to reabsorb bicarbonate is impaired, it may not be possible to fully overcome the effect of bicarbonate losses as the lowered threshold and tubular maximum (Tm) for bicarbonate are exceeded. Alkali administration should be divided into multiple, frequent doses. Sodium restriction or hydrochlorothiazide (1.5–2 mg/kg/day) may decrease alkali requirements by increasing proximal HCO_3^- reabsorption. Potassium losses increase with alkali replacement. Therefore, some, or all of the replacement alkali should be given as the potassium salt, such as potassium citrate.

The primary treatment of Fanconi syndrome is to treat the underlying cause, such as cysteamine for cystinosis, NTBC for tyrosinemia, penicillamine for Wilson disease, avoidance of galactose in galactosemia, and avoidance of fructose in hereditary fructose intolerance. In patients where the primary disease cannot be corrected, supplemental phosphate (Neutraphos), vitamin D (calcitriol), and sodium and potassium supplements must be given in addition to bicarbonate.

Prognosis of PRTA

The prognosis of PRTA is dependent on the underlying cause. Isolated PRTA can be transient, and supplemental alkali for a period of time to preserve growth is all that is necessary. In others, the PRTA is lifelong and supplemental alkali is necessary to preserve bone mineralization. The prognosis in children with Fanconi syndrome is dependent on the cause of the Fanconi syndrome. Wilson disease, tyrosinemia, galactosemia, and hereditary fructose intolerance can have a relatively good prognosis with early intervention. Early therapy with cysteamine in children with cystinosis is clearly beneficial, although the long-term prognosis for preservation of renal function is unclear.[26] To date, there is no or only incomplete therapy directly aimed at patients with Lowe syndrome or mitochondrial myopathies. Outcome of acquired Fanconi syndrome is dependent on the extent of tubular injury at the time the disorder is discovered, with some patients having only transient disease and others permanent.

Distal renal tubular acidosis

DRTA was the first to be recognized, and so has been historically named RTA type 1.[27–29] Childhood presentation of DRTA includes vomiting, failure to thrive, life-threatening metabolic acidosis, and hypokalemia. Less commonly, children with DRTA present with nephrocalcinosis, renal calculi (at times as staghorn calculi), or bone disease. In children the bone disease is rickets and in adults it is osteomalacia. Adults with DRTA commonly present with renal calculi or with musculoskeletal complaints.

Inherited forms of DRTA

Distal RTA can be inherited as an autosomal dominant or recessive trait (Table 20.4). Most families with autosomal dominant DRTA have a defect in SLC4A1, a gene on chromosome 17, which encodes for the HCO_3^-/Cl^- exchanger, AE1.[30–32] Autosomal recessive DRTA has been associated mainly with defects in the B1 and a4 subunits of the H^+-ATPase pump on

Table 20.3 Commonly available alkali replacement therapies

Name	Composition	Amount of alkali
Sodium bicarbonate tablets:	Sodium bicarbonate	
• 325 mg		4 mEq
• 650 mg		8 mEq
Sodium bicarbonate powder		~60 mEq/teaspoon
Bicitra, Shohl solution	Sodium citrate	1 mEq/ml
PolyCitra	Sodium and potassium citrate	2 mEq/ml
PolyCitra K	Potassium citrate	2 mEq/ml
Urocit-K tablets	Potassium citrate	5 mEq or 10 mEq

Table 20.4 Distal renal tubular acidosis (defective acid secretion)

Genetic:
- Autosomal dominant (AE1 deficiency)
- Autosomal recessive
- With deafness (β1 subunit of H^+-ATPase)
- Without deafness (α4 subunit of H^+-ATPase)
- Ovalocytosis with AE1 mutation (Thailand)

Hereditary diseases with DRTA:
- Hereditary elliptocytosis
- Ehlers–Danlos syndrome
- Sickle cell disease
- Familial hypercalciuria
- Type 1 glycogen storage disease
- Carnitine palmitoyl transferase deficiency
- Medullary cystic disease
- Nephronophthisis

Hypercalciuria with nephrocalcinosis:
- Primary hyperparathyroidism
- Hyperthyroidism
- Medullary sponge kidney
- X-linked hyperphosphatemia
- Fabry disease
- Vitamin D intoxication
- Wilson disease
- Hereditary fructose intoxication
- Idiopathic hypercalciuria

Autoimmune disease:
- Sjögren syndrome
- Hyperglobulinemic purpura
- SLE
- Primary biliary cirrhosis
- Chronic active hepatitis

Drug- and toxin-induced DRTA:
- Amphotericin
- Cyclamate
- NSAIDs nephropathy
- Lithium
- Foscarnet

Tubulointerstitial disease:
- Chronic pyelonephritis
- Obstructive nephropathy
- Acute and chronic renal transplant rejection
- Leprosy
- Hyperoxaluria
- Vesicoureteral reflux nephropathy

Functional (decreased sodium delivery):
- Volume contraction (U_{Na} < 10 mEq/L)
- Edema forming states:
  Nephrotic syndrome
  Cirrhosis
  Congestive heart failure

Rate-dependent (able to lower urine pH; decreased urine–blood PCO_2)

the α-intercalated cell.[33,34] ATP6V1B1 gene encodes the B1 subunit on chromosome 2. This subunit is also important in maintaining the endolymph on the cochlea pH at 7.4, and patients with this genetic defect usually have bilateral sensineural hearing loss. ATP6V0A4 gene on chromosome 7 encodes the a4 subunit of the H^+-ATPase pump. Children with this gene mutation have preserved hearing, but with long-term follow-up, mild hearing impairment has become evident in older patients with this mutation.

A few recessive kindreds from Thailand with mutations in AE1 in association with ovalocytosis have also been described.[35,36] Other genetically transmitted diseases associated with DRTA include Ehlers–Danlos syndrome,[37] hereditary elliptocytosis,[38] sickle cell disease,[39] familial hypercalciuria,[40,41] type 1 glycogen storage disease,[42] carnitine palmitoyl transferase type I deficiency,[43] and medullary cystic disease.

Pathophysiology of DRTA

Impaired H^+ ion secretion in the CCT and MCT leads to decreased ammonium and titratable acid excretion and increased bicarbonate excretion, all of which cause metabolic acidosis. The hallmark of DRTA is the inability to lower urine pH below 5.5 in the face of systemic acidosis. In young children with DRTA, the FE HCO_3 may range from 5 to 15%, leading to potentially life-threatening acidosis.[27,29] This higher FE HCO_3 in children compared to adults with DRTA requires a larger alkali requirement, especially to maintain normal growth. After age 4–5 years, there is a decrease in the alkali need to levels seen in adults. Acidosis in DRTA is associated with significant renal sodium wasting, leading to increased renin and aldosterone secretion, and hypokalemia that can be profound. Correction of the acidosis usually leads to a reduction in these electrolyte losses. Volume contraction and salt wasting is especially common in patients with nephrocalcinosis and tubulointerstitial disease.

The chronic metabolic acidosis leads to buffering of H^+ by bone, and impaired bone mineralization. This causes rickets in children and osteomalacia in adults.[27,29,44] Correction of the metabolic acidosis reverses this type of bone disease.[45] Chronic acidosis in DRTA is associated with decreased renal citrate production, which causes hypocitraturia.[46] Hypocitraturia with increased urinary calcium excretion from the metabolic acidosis predisposes to nephrocalcinosis and nephrolithiasis.[27–29] Nephrocalcinosis impacts net acid excretion negatively by impairing transfer of NH_4^+ from the loop of Henle into the collecting duct. Ongoing nephrocalcinosis and recurrent calcium phosphate/oxalate stone disease can cause progressive loss of renal function. Alkali therapy decreases urinary calcium excretion and increases citrate excretion, reducing the risk of further nephrocalcinosis and stone formation. However, nephrocalcinosis, if present before alkali therapy is instituted, does not resolve with correction of acidosis. Chronic metabolic acidosis also interferes with growth, and failure to thrive and short stature are common findings in children with untreated DRTA.[27–29]

Autoimmune disorders, especially Sjögren syndrome, have been associated with DRTA.[47–50] Nephrocalcinosis from any cause can also lead to DRTA. Buckalew described a large family in which the hypercalciuria and nephrocalcinosis preceded the development of DRTA.[40] Medullary sponge kidney is associated with DRTA, suggesting that cystic dilatation of the collecting tubules can impair acid excretion.[51] Chronic medullary injury from sickle cell disease is also associated with DRTA.[39]

Markedly reduced distal sodium delivery, manifested by urine Na^+ concentration below 10 mmol/L, impairs voltage-dependent H^+ secretion in the CCT and inability to lower urine pH < 5.5.[52,53] This is a functional RTA since expanding volume in patients with dehydration or increasing distal sodium delivery with furosemide or a non-reabsorbable anion like sulfate in patients with edema-forming states, nephrotic syndrome, congestive heart failure, or cirrhosis, will restore the distal nephron's ability to acidify and excrete ammonium.

Strife et al[54] described a group of young children who had mild hyperchloremic metabolic acidosis but were able to lower their urine pH below 5.5. Most had poor linear growth, and two of the seven patients described also had nephrocalcinosis. Although they could generate a low urine pH, they were unable to raise their urine PCO_2 above blood PCO_2, indicating rate-dependent RTA as proposed by Batlle at al.[55] During follow-up, none of the patients with rate-dependent RTA have progressed to more severe RTA, and a number have been able to discontinue alkali supplementation, altogether.

A number of medications have been implicated in impaired distal H^+ excretion. Amphotericin B alters the permeability of the distal nephron, allowing back-leak of H^+ from lumen to blood.[56] This dissipates the H^+ gradient (gradient defect RTA) and limits H^+ excretion. Lithium carbonate impairs H^+ secretion but this usually does not result in disease.[57] Large doses of cyclamate and non-steroidal anti-inflammatory drugs (NSAIDs) impair H^+ secretion.[58,59] Foscarnet has also been shown to decease distal acidification.[60]

Tubulointerstitial diseases can also cause distal RTA. These include transplant rejection,[61–63] obstructive uropathy,[64,65] vesicoureteral reflux,[66] hyperoxaluria,[67] leprosy,[68] and pyelonephritis, especially if associated with urolithiasis.[69]

Treatment of DRTA

Patients with DRTA usually require only 1–3 mEq/kg/day alkali supplementation to correct the metabolic acidosis, often correcting kaliuresis and naturesis as well.[27–29] Infants and young children require larger doses of alkali supplementation for optimal growth, usually 2–4 mEq/kg/day, but at times more than 5 mEq/kg/day.[27–29,70] The larger doses are needed because of increased endogenous acid production and bicarbonate loss in young children with DRTA. Some patients require potassium supplementation, in addition to alkali therapy. When patients with DRTA present with severe metabolic acidosis and hypokalemia, initial therapy should be directed at treating the hypokalemia before treating the acidosis, since correcting the acidosis first may worsen hypokalemia and cause respiratory depression.

Prognosis of DRTA

With adequate treatment, normal growth can be achieved and bone disease prevented or reversed. Early treatment is necessary to prevent nephrocalcinosis, which can lead to renal insufficiency. After age 4–5 years, there is less bicarbonate loss and lower doses of alkali are necessary to maintain correction (1–2 mmol/kg/day).

Type IV renal tubular acidosis

Type IV RTA is the most common form of RTA and is caused by numerous disorders (Table 20.5). Patients with Type IV RTA present with hyperkalemia and mild metabolic acidosis. They are able to acidify the urine pH below 5.5. Patients with type IV RTA often have signs and symptoms of aldosterone deficiency or resistance. Infants with type IV RTA often present with failure to thrive.

Pathophysiology

Type IV RTA is caused by hyperkalemia associated with aldosterone deficiency or resistance. Hyperkalemia decreases proximal tubule ammonia production and competes with NH_4^+ for the $Na^-/2Cl^-/K^+$ transporter in the ascending limb of the loop of Henle, reducing the medullary ammonium gradient. Hyperkalemia also impairs the entry of NH_4^+ into the MCT cell from the medullary interstitium via the K^+ secretory site on the basolateral membrane Na^+/K^+-ATPase. The net effect is decreased NH_4^+ and net acid excretion. Aldosterone deficiency or resistance decreases H^+ secretion in the collecting duct by decreasing the number and function of H^+-ATPase pumps. Aldosterone is also important for increasing the negativity of the lumen of the CCT by enhancing the absorption of Na^+ via the apical membrane epithelial sodium channel (ENaC) and the basolateral membrane Na^+/K^+-ATPase. The increased lumen negativity facilitates H^+ secretion into the lumen of CCT.

Inherited forms of type IV RTA

Several autosomal recessive genetic disorders of adrenal steroid synthesis lead to decreased or absent aldosterone synthesis. The most common is 21-hydroxylase deficiency, coded for by the genes on chromosome 6.[71,72] Rarer genetic aldosterone synthetic defects include 3β-hydroxysteroid dehydrogenase, coded for on chromosome 1, corticosterone methyl oxidase I and II, and congenital lipoid adrenal hyperplasia or StAR deficiency, coded for on chromosome 8.[72,73]

Autosomal dominant pseudohypoaldosteronism I (PHAI) is associated with hyperkalemia, salt wasting, elevated renin and aldosterone levels, and hypotension. Autosomal dominant

Table 20.5 Causes of type IV renal tubular acidosis

Aldosterone deficiency:
- Addison disease
- Bilateral adrenalectomy
- Congenital adrenal hyperplasia
- 21-hydroxylase deficiency
- 3β-hydroxysteroid dehydrogenase
- Corticosterone methyl oxidase I and II deficiency
- Congenital lipoid adrenal hyperplasia (StAR deficiency)
- ACE inhibitors
- Hyporeninemic, hypoaldosteronism
- Diabetic nephropathy
- AIDS nephropathy
- Gouty nephropathy
- Tubulointerstitial nephritis
- NSAIDs
- β-blockers
- Hypoaldosteronism of critical illness
- Heparin
- Pseudohypoaldosteronism II – Gordon syndrome (WNK1 and -4 mutations)

Aldosterone resistance:
- Autosomal dominant pseudohypoaldosteronism I (aldosterone receptor defect)
- Autosomal recessive pseudohypoaldosteronism I (ENaC defect)
- Tubulointerstitial disease
- Fetal alcohol syndrome
- Sickle cell nephropathy
- Renal transplant rejection
- Obstructive uropathy
- Renal dysplasia
- Analgesic nephropathy
- Nephrocalcinosis/nephrolithiasis
- SLE
- Drugs that interfere with aldosterone receptor:
  - Spironolactone
- Drugs that inhibit ENaC:
  - Amiloride
  - Trimethoprim
  - Triamterene
  - Pentamidine
- Drugs that interfere with Na^+/K^+-ATPase:
  - Cyclosporine
  - Tacrolimus

PHAI is caused by a mutation in the mineralocorticoid receptor in the collecting tubule.[74] The mutant mineralocorticoid receptor is unable to respond to aldosterone properly and this leads to a decrease in the activity of the ENaC. This in turn decreases luminal Na^+ absorption and the transepithelial potential difference. The decreased potential difference reduces K^+ and H^+ secretion.[74] Supplemental mineralocorticoid therapy will not correct the defect. However, carbenoxolone, an 11β-hydroxysteroid dehydrogenase inhibitor, can raise intracellular cortisol levels and overcome the functional defect in the mineralocorticoid receptor. The clinical features became less severe as the child ages.

Autosomal recessive PHAI is caused by a defective EnaC.[75,76] Infants with recessive PHAI have severe hyperkalemia, salt wasting, type IV RTA, and hypotension. Renin and aldosterone levels are quite elevated. Newborns with recessive PHAI may have respiratory distress due to impaired Na^+ and water reabsorption from the alveoli resulting from defective ENaC in the alveolar membranes.[77] The defective ENaC is unable to properly transport luminal Na^+, leading to decreased luminal negativity and decreased K^+ and H^+ secretion into the lumen.

Gordon syndrome, or pseudoaldosteronism II (PHAII), is a rare autosomal dominant disorder characterized by hypertension, hyperkalemia, low renin and aldosterone levels, type IV RTA, and mild volume expansion.[78] Previously, PHAII was thought to result from an early distal tubule 'chloride shunt'. It is now known to be caused by mutations in WNK1 and 4 proteins.[79] WNK4, coded on chromosome 17, inhibits the NaCl cotransporter in the DCT and the ROMK channel, and the paracellular permeability of Cl^-. Mutations in WNK4 increase the activity of the NaCl cotransporter and paracellular Cl^- permeability, but further inhibit ROMK activity, leading to volume expansion, hyperkalemia, and voltage-dependent type IV RTA. How WNK1 mutations cause a similar clinical syndrome is unclear. Thiazide diuretics correct the hyperkalemia, acidosis, and hypertension.

Acquired hypoaldosteronism and aldosterone resistance

Diseases of the adrenal gland can lead to type IV RTA, including autoimmune adrenal failure, tuberculosis, fungal infection, or AIDS. Isolated hypoaldosteronism can occur in critically ill patients and is thought to be related to inhibition of aldosterone synthetase by hypoxia, cytokines, atrial natriuretic peptide, and heparin.[80] Hypoaldosteronism leads to hyperkalemia and type IV RTA. Type IV RTA from hyporeninemic hypoaldosteronism is also seen in older patients with renal insufficiency from diabetic nephropathy, AIDS, SLE, and tubulointerstitial nephritis.[81] The hyporeninemia does not respond to the usual measures to stimulate renin secretion, but low aldosterone levels increase with the infusion of angiotensin II.

Tubulointerstitial diseases may also cause unresponsiveness to aldosterone, leading to hyperkalemia and metabolic acidosis from decreased ammonium excretion. Such tubulointerstitial diseases include analgesic abuse, sickle cell disease, nephrolithiasis, nephrocalcinosis, acute and chronic transplant rejection, and systemic lupus erythematosus (SLE). Infants with fetal alcohol syndrome may have mild-type IV RTA.[82] Obstructive uropathy and renal dysplasia are also common causes of type IV RTA and relative tubular unresponsiveness to aldosterone in children.[64,65,83,84]

A number of drugs can cause type IV RTA. NSAIDs can cause hyperkalemia and metabolic acidosis by inhibiting renin release.[85] β-blockers similarly inhibit renin release as well as

altering potassium distribution. Heparin can be directly toxic to the zona glomerulosa and inhibit aldosterone synthase.[86] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers both lead to hypoaldosteronism and can cause hyperkalemia and acidosis, especially in patients with renal insufficiency. Spironolactone is a competitive inhibitor of aldosterone and also can cause hyperkalemia and metabolic acidosis.[87] Amiloride, triamterene, trimethoprim, and pentamidine inhibit the ENaC channel in the collecting duct principal cell.[88–90] This lowers the transepithelial potential difference, reducing the secretion of H^+ and K^+. The resulting hyperkalemia reduces ammonium production and excretion. Cyclosporine and tacrolimus cause hyperkalemia and metabolic acidosis through inhibition of basolateral Na^+/K^+-ATPase.[91,92] This decreases intracellular K^+ concentration and the transepithelial potential, lowering the driving force for K^+ secretion in the CCT.

Diagnosis of type IV RTA

The responsiveness of the CCT to aldosterone in the setting of hyperkalemia can be evaluated by the transtubular potassium gradient (TTKG); i.e. the potassium gradient between the peritubular capillary and the CCT lumen.[93] The TTKG is defined as:

$$\text{TTKG} = \frac{[K^+\text{urine}]/[K^+\text{plasma}]}{U_{osm}/P_{osm}} \qquad (7)$$

TTKG ≥ 8 indicates that adequate aldosterone is present and that the CCT is responding appropriately in the hyperkalemic patient; TTKG < 8 suggests aldosterone deficiency or tubular unresponsiveness. Patients with aldosterone deficiency will increase their TTKG after several days of therapy with fludrocortisone, whereas those with tubular insensitivity fail to do so. Although the TTKG is a useful clinical test, it tends to underestimate the K^+ secretory capacity in the hyperkalemic patient with a dilute urine or polyuria.

Treatment of type IV RTA

Treatment in type IV RTA is based on the underlying etiology. A careful history of drug use is important to identify potential offending pharmaceutical or toxic agents. Evaluation of plasma renin activity, aldosterone secretion, and TTKG are useful to distinguish aldosterone deficiency from tubular unresponsiveness. Patients with glucocorticoid and mineralocorticoid deficiency need replacement steroids. Patients with hyporeninemic hypoaldosteronism may benefit from a loop diuretic and cation exchange resin to increase potassium excretion. Supraphysiologic doses of fludrocortisone may be helpful, but can cause volume overexpansion and hypertension.

Infants with PHAI should receive salt supplements to correct the volume depletion. In contrast, patients with PHAII should be treated with thiazide diuretics with salt restriction. Patients with tubular resistance to aldosterone and hyperkalemia should be treated with dietary K^+ restriction and loop diuretics to increase K^+ secretion and augment transepithelial potential difference. Cation exchange resins to decrease the hyperkalemia may also be helpful. Supplemental alkali can be used to treat the acidosis.

Type III RTA

After the description of types I and II RTA, it was recognized that some infants and young children had the inability to acidify their urine in the face of severe acidosis and also had significant urinary bicarbonate losses, in the range of 5–10% of the filtered load.[27,29,70] A few of these infants had a fractional bicarbonate loss as high as 15%. This combined pattern suggested both a proximal and distal nephron dysfunction, and was termed type III RTA. It was recognized later that the bicarbonate loss became much less after the child was 4–5 years old and the abnormality was consistent with type I or DRTA. Whether this disorder primarily reflects proximal or distal tubular dysfunction is still unclear. More recently, an autosomal recessive disorder characterized by mental retardation, cerebral calcifications (marble brain disease), acidosis, and osteopetrosis has been described in association with deficiency of CAII.[20] CAII is in the cytoplasm of a number of cells, including proximal and distal tubule cells as well as osteoclasts. Defective CAII function impairs the ability of the cell to combine water and CO_2 to form H^+ and HCO_3^- for reclamation of filtered bicarbonate in the proximal tubule, and acidification and bicarbonate regeneration in the distal tubule. H^+ secretion by the osteoclast is also important for bone remodeling. CAII deficiency appears to be a true example of type III RTA.

Evaluation of a child for possible RTA

The initial step in the evaluation is to ascertain that the child has acidosis (see Figure 20.5). Most children with a low serum HCO_3^- will have metabolic acidosis. The history and physical examination should support that diagnosis. If there is doubt, a blood gas showing a low pH and CO_2 will confirm this suspicion. Next, the serum anion gap should be determined by Eqn 3. If the anion gap is between 8 and 16 mEq/L (normal anion gap metabolic acidosis), then RTA is a possibility. If the anion gap is elevated, then some other cause of metabolic acidosis must be sought, such as renal failure, DKA, or another organic acidosis.

The next step in normal anion gap acidosis, or HCMA, is to measure the urine net charge (urine anion gap) (Eqn 4) to determine if there is an appropriate increase in urine ammonium excretion. If the net charge is negative, then the cause

of the acidosis is extrarenal, such as gastrointestinal loss of HCO_3^-. If the anion gap is positive, then the patient has RTA.

To determine the type of RTA, the following next steps are helpful. Measure serum K^+. If the serum K^+ is high, the low urine NH_4^+ concentration is a consequence of hyperkalemia (type IV RTA). Measurement of serum renin and aldosterone and the TTKG are useful in determining whether the hyperkalemia is from hypoaldosteronism or resistance. A high urine pH (>5.5) indicates an associated H^+ secretion problem (voltage defect). If the urine Na^+ is less than 10 mEq/L, then the RTA is a function of either volume contraction or an edema-forming state. If volume contraction is present, the RTA can be corrected with volume expansion. If the RTA is from an edema-forming state, then maneuvers to increase distal sodium delivery, such as the administration of furosemide, will improve the acidosis.

If the serum K^+ is low, then the next step is to determine the urine pH and fractional excretion of HCO_3^- with alkali loading. A low urine pH during spontaneous acidosis along with a high urinary fractional excretion of HCO_3^- (>10–15%) suggests PRTA. The presence of glucosuria, hypophosphatemia, and aminoaciduria, along with the HCMA and hypokalemia, suggests a global proximal tubule disorder, Fanconi syndrome. A urine pH >5.5 in the face of acidosis suggests DRTA. A FE HCO_3 >10% is common in infants and young children with DRTA. High FE HCO_3 with an alkaline urine pH is also seen in patients with osteopetrosis from CAII deficiency. Further confirmation of DRTA can be made by demonstrating a low urine–blood PCO_2 during HCO_3^- loading or after acetazolamide.

From the principles described in this chapter, an idealized set of curves can be drawn predicting the relationship between urine pH and serum bicarbonate in normal subjects and in patients with PRTA or DRTA after acute acid loading (see Figure 20.6). Urine pH reflects the ability of the distal nephron to generate a hydrogen ion (H^+) concentration gradient. A maximal normal response to acute acidosis is a gradient of 1:1000 (blood to lumen) or a urine pH of ~4.5. A linear relationship holds between urine pH and serum bicarbonate over the normal range of serum bicarbonate values. When the upper limit of normal serum bicarbonate is reached (urine pH 7.5–8.0), the curve flattens and this is the Tm for bicarbonate reabsorption. The point when the urine pH rises rapidly as the serum bicarbonate is increased is the bicarbonate threshold. Thus, a sigmoid curve is described. With chronic acidosis, ammoniagenesis is maximized and the urine pH is higher because a much greater percentage of the net acid excreted is excreted as ammonium ion. Patients with PRTA are able to generate a hydrogen ion gradient but, because their threshold and often their Tm are lowered, this idealized sigmoid curve is shifted to the left. In DRTA, defective urinary acidification causes the urine pH to match the plasma pH. These idealized curves were confirmed through clinical and experimental studies by Rodriguez Soriano and colleagues[12] over a wide range of serum bicarbonate values.

Illustrative cases

Case 1

An 8-month-old infant was noted to be failing to thrive. Serum electrolytes showed a Na^+ 140, K^+ 3.5, Cl^- 114, and HCO_3^- 14 mEq/L. His urine electrolytes were Na^+ 88, K^+ 13, Cl^- 78 mEq/L, and his urine pH was 5.1. The urinalysis had no glycosuria or proteinuria. Urine amino acids were normal. He was started on supplemental alkali and his serum HCO_3^- rose to 24 mEq/L after giving him 8 mEq/kg/day. His urine pH rose to 8 and his urinary fractional HCO_3^- excretion was 18%.

Comment

This patient had HCMA with a normal anion gap. The urine net charge was positive, indicating low excretion of ammonium and RTA. During spontaneous acidosis, the urine pH was low. With correction of the acidosis, the fractional HCO_3^- excretion was very high, suggesting PRTA. The lack of aminoaciduria, glycosuria, and proteinuria indicates that this is isolated PRTA.

Case 2

A 6-year-old boy presented to the emergency room with a blood pH of 7.10. His serum electrolytes were Na^+ 136, K^+ 2.5, Cl^- 116, and HCO_3^- 8 mEq/L. His urine electrolytes were Na^+ 72, K^+ 31, Cl^- 70 mEq/L, and his urine pH was 6.2. A renal ultrasound showed nephrocalcinosis. He required 3 mEq/kg/day of alkali to maintain a normal serum HCO_3^- and at this point his urinary fractional HCO_3^- excretion was 3%. A urine–blood PCO_2 test showed only a difference of 2 mmHg.

Comment

This patient again had HCMA with a normal anion gap. The positive net urine charge indicates RTA. The alkaline urine pH in the face of marked acidosis suggests DRTA and the low urine–blood PCO_2 confirms it. Nephrocalcinosis is common in untreated DRTA.

Case 3

A 3-month-old infant presented to the emergency room with dehydration from diarrhea and a blood pH of 7.2. The serum electrolytes showed Na^+ 135, K^+ 3.5, Cl^- 110, and HCO_3^- 11 mEq/L. His urine electrolytes were Na^+ 3, K^+ 6, Cl^- 16 mEq/L, and his urine pH was 6.0.

Comment

Again, this patient had normal anion gap acidosis. The urine pH was relatively alkaline in the face of significant acidosis. However, the urine net charge was negative, indicating increased ammonium excretion and an appropriate response to the acidosis. The alkaline urine is secondary to decreased Na^+ delivery to the CCT for H^+ excretion. With restoration of the extracellular volume, a urine–blood PCO_2 test was normal with a difference of 30 mmHg.

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21 Disorders of tubular transport

Paul Goodyer

During passage of tubular fluid down each renal tubule, solutes are reabsorbed by the highly selective transport mechanisms that are arranged in series along the successive nephron segments (Figure 21.1). In general, high-capacity transport occurs in the proximal tubule where the luminal membrane forms an elaborate 'brush border' of microvilli to provide extensive surface area for the reabsorptive processes. Energy for active transport is provided by densely packed mitochondria arrayed toward the basolateral surface. Organic solutes such as low-molecular-weight proteins, sugars, and amino acids are avidly (>98%) reabsorbed in this segment. Whereas bulk transport of inorganic solutes and water is also accomplished in the proximal tubule, a substantial fraction of the filtered load also arrives at more distal sites. High-affinity, lower-capacity transport mechanisms in this region fine-tune the net reabsorption of these solutes and water. These distal transport systems tend to be regulated by hormonal signals, which reflect solute-specific whole-body fluid and electrolyte homeostasis.

Clinical disorders of tubular function that will be discussed in this chapter are outlined in Table 21.1. First, disorders affecting reabsorptive transport in the proximal tubule will be considered. These include defects of specific transport systems as well as disorders causing broad proximal tubule dysfunction, such as the Fanconi syndrome. Secondly, the disorders of salt reabsorption affecting the distal nephron (thick ascending limb of the loop of Henle, distal convoluted tubule, and cortical collecting duct) will be addressed. These can be grouped into the diseases where salt reabsorption is excessive, causing hypertension, or those in which reabsorptive defects cause salt wasting or isolated divalent cation wasting. Finally, acquired and hereditary disorders of water reabsorption in the cortical and medullary collecting duct will be discussed.

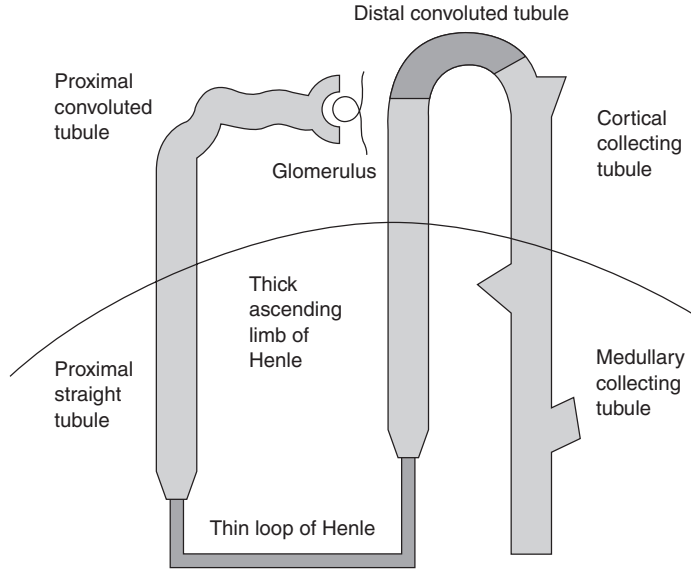

Figure 21.1 Schematic diagram of renal tubular segments associated with human transport disorders.

Selective transport defects of proximal tubules

Cystinuria

Cystinuria is a hereditary disorder characterized by nephrolithiasis. It accounts for 10–15% of all urinary stones in children. Cystinuria was first described by Wollaston in 1803, who extracted a large golden brown bladder stone from one of his patients. In characterizing its chemical properties, he considered the stone to be formed of an oxide secreted by the bladder wall. Wollaston referred to the substance as 'cystic oxide', making reference to the Greek word *kyst* for bladder. When chemical analysis of these stones was finally possible, the principal ingredient of these stones, an amino acid, was named 'cystine', making reference to Wollaston's original discovery.

Pathophysiology

Cystinuria is caused by a defect in the reabsorptive transport of cystine (Figure 21.2) and dibasic amino acids (ornithine, arginine, and lysine) at the luminal brush border membrane of the renal proximal tubule.[1] Normally, about 98–99% of the filtered load of these amino acids is reabsorbed during transit through the proximal tubule, but in classic cystinuria the entire filtered load escapes proximal tubular reabsorption and arrives

Table 21.1 Classification of tubular disorders

Proximal tubular disorders

Selective transport defects:
- Cystinuria
- Hartnup disease

Fanconi syndrome:
- Cystinosis
- Dent disease
- Lowe syndrome
- Tyrosinemia
- Wilson disease
- Galactosemia
- Fructosemia
- Mitochondrial cytopathies

Disorders of distal nephron

Salt-wasting defects:
- Bartter syndrome
- Gitelman syndrome
- Pseudohypoaldosteronism

Excess salt-retaining defects:
- Liddle syndrome
- Glucocorticoid-remediable aldosteronism
- Gordon syndrome
- Syndrome of apparent mineralocorticoid excess

Disorders of magnesium reabsorption
- Familial hypomagnesemia with hypercalciuria (FHH).
- Hypomagnesemia with severe hypocalcemia (HSH)

Disorders of water reabsorption
- Nephrogenic diabetes insipidus

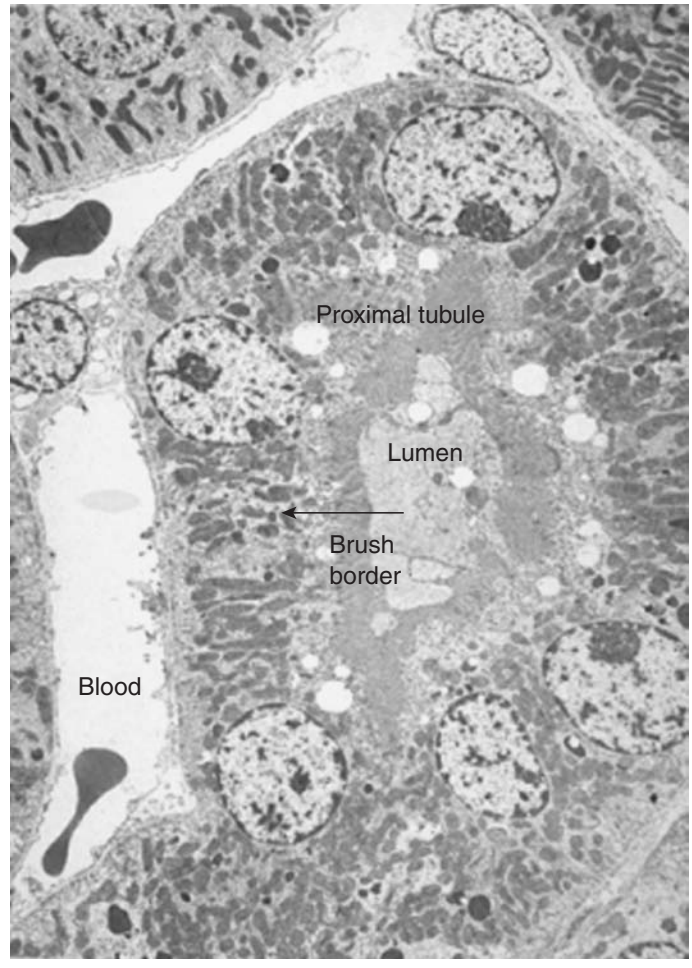

Figure 21.2 Electron microscopic picture of a cross-section of proximal renal tubule showing direction (arrow) of cystine, ornithine, arginine, and lysine uptake from lumen into the cell via the brush border membrane. Cystine and the dibasic amino acids exit the cell into peritubular capillaries via distinct transporters at the basolateral membrane.

at distal sites where tubular fluid is progressively acidified. Since cystine is poorly soluble in an acidic urine, when the threshold of cystine solubility in acid urine is exceeded, cystine (but not the dibasic amino acids) comes out of solution, and leads to crystalluria (Figure 21.3). During periods of low tubular flow and/or lack of endogenous stone inhibitors, cystine microcrystals coalesce into solid stones (Figure 21.4) within the urinary tract, leading to renal colic and hematuria in these children.

Genetics

The incidence of cystinuria is about 1:7000 worldwide, but cystinuria is encountered more frequently in certain populations, such as Libyan Jews (1:2500), where genetic founder effects pertain. In the 1950s, Harris measured urinary cystine excretion by parents of affected probands, and showed that families conformed to two basic patterns.[2,3] In the first type, cystine excretion by each heterozygous parent was within the normal range, implying a fully recessive pattern of inheritance. However, in other families, both parents had moderately elevated urinary cystine, although not usually in the stone-forming range of the homozygous offsprings.[2,3] Thus, in these families, the disorder was transmitted as a dominant trait.

The gene mutations responsible for cystinuria have been well characterized. In the 1990s, it was found that patients with recessive cystinuria in Europe, the Middle East, and North America had inherited two mutant copies of the *SLC3A1* gene on chromosome 2p21.[4–6] The *SLC3A1* gene encodes a subunit of the cystine transport mechanism present in the proximal tubule brush border. Heterozygotes carry only one mutant *SLC3A1* gene and always excrete cystine in the normal range, whereas homozygotes typically excrete 2000–5000 μmol cystine/g creatinine.[7] In 1997, the International Cystinuria Consortium demonstrated that dominant cystinuria is caused by mutations of the *SLC7A9* gene on chromosome 19, which encodes the luminal cystine transport channel. Heterozygotes usually excrete cystine in the range of 100–1000 μmol/g creatinine, whereas homozygotes typically excrete cystine at levels similar to *SLC3A1* homozygotes (2000–5000 μmol/g creatinine).[8] Interestingly, 10–15% of cystinuria patients have

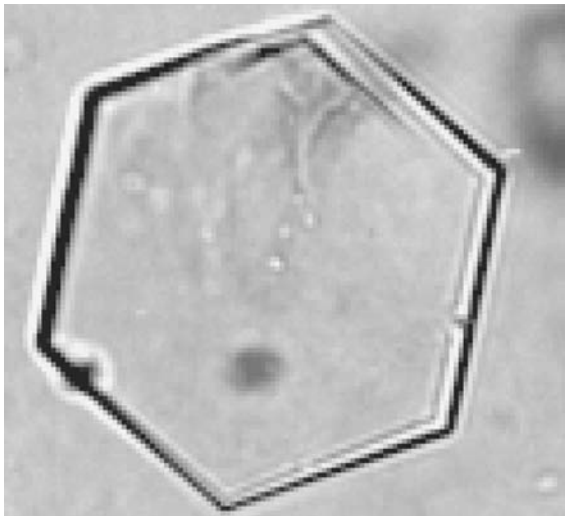

Figure 21.3 Light microscopy of urinary sediment showing characteristic hexagonal cystine crystal. Under appropriate conditions, the crystals may coalesce into large calculi.

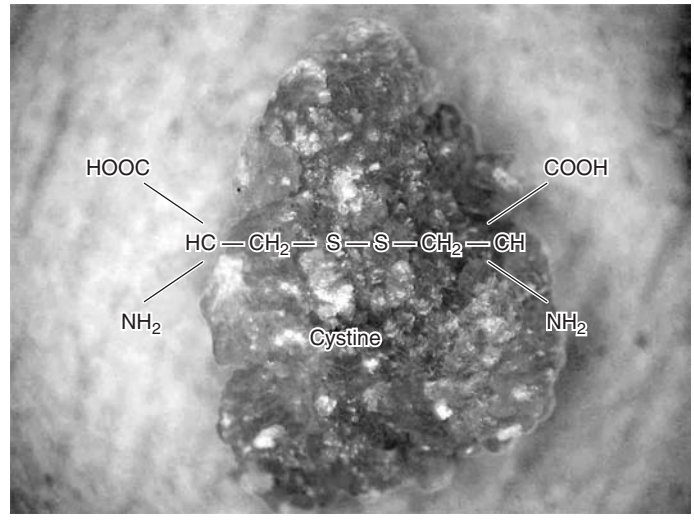

Figure 21.4 Photograph of a cystine stone. The stone was pale yellow in color. The chemical structure of cystine is also shown.

relatively mild missense mutations (e.g. A182T) of *SLC7A9*, mimicking the recessive phenotype.[9,10] Furthermore, a small number of patients (2–3%) have a genetically 'mixed type' of digenic cystinuria caused by a combination of *SLC3A1* and a *SLC7A9* mutations.[10] The risk of stone formation is equally high in homozygous recessive or dominant cystinuria, but cystine excretion level and stone risk is lower in the mixed form.[7]

Nearly 75% of infants who appear to have homozygous cystinuria in the newborn period are later found to be heterozygotes for the dominant type of cystinuria (transient neonatal cystinuria) and are highly unlikely to form stones. When tubular transport has fully matured (by 1–2 years of age), these patients can be easily distinguished from true homozygotes. In the latter, recurrent cystine nephrolithiasis begins early in life.

Clinical manifestations

Recurrent urolithiasis is the sole manifestation of cystinuria. During the first 5 years, these patients are usually stone-free, despite high urinary cystine levels. However, during the second half of the first decade, about 50% of affected children develop their first stone, and another 25% begin to form stones during their teens.[7] In a study of 29 adult cystinuria patients treated with high fluid intake and alkalinization, Barbey calculated that about 1 new stone is formed per patient-year and each patient has an average of one surgical procedure every 3 years.[11] By middle age, the average cystinuria patient has undergone 7 surgical procedures for nephrolithiasis.[12] Acute obstruction of the urinary tract by a cystine stone may cause rapid loss of renal parenchyma.[13] It is estimated that 10–30% of adult cystinurics have reduced glomerular filtration rate (GFR).[14,15]

Little is known about the factors that determine cystine crystal coalescence to form renal stones. Daudon et al recently proposed that cystine microcrystal size is a powerful predictor of nephrolithiasis risk.[16] Recurrent-stone formers have an average cystine crystal volume of 8173 μm^3 vs 233 μm^3 in non-stone-formers.[16] Treatment modality appears to alter the cystine crystal volume. Average crystal volume in the study of Daudon et al was 12 000 μm^3 in untreated patients, 2600 μm^3 with conservative therapy, 1141 μm^3 with high fluid intake and mercaptopropionyl glycylglycine therapy, and 791 μm^3 with high fluid volume and penicillamine therapy.[16]

Renal transplantation, if necessary in patients with cystinuria, is not associated with any recurrence of renal stones in the allograft, since the transplanted kidney does not have the transport defect in the proximal renal tubules.

Diagnosis

Microscopic examination of the most concentrated and acidic urine (first morning urine sample) may reveal the typical cystine crystals in asymptomatic patients. Cystine crystals have a characteristic hexagonal cystine structure (Figure 21.3) and they dissolve in alkaline urine. Chemical analysis of the stone often provides the diagnosis of cystinuria in the patient with established urolithiasis.

The cyanide–sodium nitroprusside test can be used as a screening test for cystinuria. The test is conducted by mixing urine with cyanide solution, which converts cystine to cysteine. After addition of nitroprusside solution, development of a purple color denotes abnormal cystine concentration in the urine (>75 mg/g of creatinine). False-positive test results can occur in homocystinuria, bacterial contamination, and in the presence of drugs such as penicillin, captopril, and penicillamine.

Ion exchange chromatography in a randomly collected urine sample provides an acceptable and rapid determination of cystine and dibasic amino acid concentration in urine. This test is available through several commercial laboratories.

To determine the risk for stone formation, a 24-hour collection of urine for cystine concentration may be necessary. Genetic testing, although offered through research laboratories, is not yet available commercially.

Radiologic studies such as renal and bladder ultrasound should be obtained in patients suspected of having renal stones. In addition to urinary stones, ultrasonography may also detect amorphous crystal debris in the bladder. Because of their low calcium content, cystine stones are generally radiolucent, but a faint radiopaque shadow may be evident sometimes. An intravenous pyelogram reveals a filling defect of these stones within the urinary tract. A computerized axial tomography (CAT) scan with contrast may provide the best evidence for the stone in an asymptomatic patient.

Treatment

Conservative therapy High fluid intake is recommended for all cystinuria patients.[17] Since low intake of salt and water overnight leads to an acidified urine by the morning, fluid intake and urinary alkalinizing agents at bedtime are a logical recommendation. Sodium bicarbonate or potassium citrate in the dose of 1–2 mEq/day can be given orally as urinary alkalinizing agents. The aim should be to maintain urinary pH > 7 during most times of the day. Barbey et al have recently demonstrated the benefit of high fluid intake (2 L/m^2) and alkalinization on the frequency of stone formation in adults,[11] but this 'conservative therapy' is difficult to sustain. Only 15% of adult patients with cystinuria successfully maintain urine cystine concentration below its theoretic limit of solubility in urine (300 mg/L), 15% never succeed, and the remainder succeed initially but are unable to sustain compliance.[18]

Drug therapy Because of poor compliance with conservative regimens of fluid intake and urinary alkalinization, most patients with recurrent cystine nephrolithiasis require therapy with thiol-containing drugs that form soluble mixed sulfides with cystine in urine. In the early 1960s Crawhall et al reported that oral penicillamine (15 mg/kg/day in four divided doses) is excreted in the urine and forms soluble mixed disulfides with cystine.[19] Another sulfur-containing agent, α-mercaptopropionyl glycine (MPG, Thiola) at a dose of 10–30 mg/kg/day in four divided doses has also been used to treat cystinuria.[20] There are no carefully designed clinical trials comparing the two agents, but in-vitro studies and retrospective clinical analyses indicate that both drugs work fairly well. Penicillamine was shown to reduce nephrolithiasis by 68% (from 1.6 stones/year on conservative management to 0.52 stones/year).[21] At urinary concentrations predicted from a standard dose, penicillamine reduces cystine precipitation by 90% in vitro and reduces urinary cystine crystal size to 7% of that in untreated patients.[16] MPG is almost as effective, reducing new stone formation by 60%,[21] in-vitro cystine precipitation by 57%,[13] and urinary cystine crystal size to 9.5% of that in untreated patients.[16] Barbey et al reviewed treatment of 27 adults with one or the other thiol (312 patient-years) compared with the pretreatment period of hyperdiuresis and alkalinization (217 patient-years). The incidence of new stones and operative procedures fell from 0.93 to 0.22 stones/year and 0.29 to 0.14 operations/year, respectively.[11]

Although these agents are efficacious, they are not without significant side effects. There have been no careful safety comparisons of the two drugs, but the spectrum of reported adverse effects are similar and include glomerulonephritis, proteinuria, pemphigus-like dermatopathy, myopathy/myasthenia gravis, systemic lupus erythematosus (SLE)-like syndromes, hyperlipidemia, cholestatic jaundice, loss of taste, rash, and fever.

Recently, captopril, an angiotensin-converting enzyme inhibitor that also contains thiol, has been proposed as an alternative therapy for cystinuria. Captopril has little effect on cystine precipitation in vitro[13] and has no effect on crystal volume in patient urine.[16] In vivo, however, captopril reduces cystine excretion slightly, but the dose required for prevention of cystine nephrolithiasis often results in symptomatic hypotension.[21]

Surgery When surgical intervention is required, percutaneous nephrolithotomy has a good (> 90%) success rate but complications (bleeding, perforation of the collecting system) are not insignificant, particularly with staghorn calculi and among children < 7 years of age.[22] Furthermore, urinary obstruction can lead to eventual reduction in GFR,[22] and such a risk correlates with the number of surgical interventions.[23] Extracorporeal shockwave lithotripsy (ESWL) in children may require general anesthesia. Cystine stones are harder to disrupt with ESWL. Despite this, the success of the ESWL procedure is acceptable in older children with pelvic and ureteral stones; however, it is poor in calyceal stones.[12]

Hartnup disease

Hartnup disease is an autosomal recessive disorder characterized by episodes of pellagra-like skin rash, cerebellar ataxia, and emotional volatility due to defective intestinal and proximal renal tubular reabsorption of neutral amino acids. In newborn screening programs, its incidence is about 1:26 000.[24] Many patients remain asymptomatic for long periods, suggesting that symptomatic episodes may be precipitated by environmental factors, such as inadequate diet or increased metabolic needs.[25] Clinical manifestations represent deficient intestinal uptake of dietary neutral amino acids (particularly tryptophan), rather than renal amino acid losses, and symptoms of nicotinamide deficiency arise due to tryptophan depletion.[26] Recent genetic linkage studies suggest that the Hartnup chromosomal locus is localized at 5p15, but the specific gene involved has not been identified. Since symptoms are episodic, preventive nicotinamide supplementation is indicated.

Fanconi syndrome

Fanconi syndrome refers to a severe proximal tubular dysfunction that is characterized by bicarbonaturia, metabolic acidosis, hypokalemia, glycosuria, phosphaturia, aminoaciduria, and

low-molecular-weight proteinuria. Patients often develop rickets due to hypophosphatemia. The defect can be partial, or associated with varying combinations of reabsorptive deficits. Fanconi syndrome does not include isolated renal glycosuria. Cystinosis is a common cause of an inherited type of Fanconi syndrome, although acquired forms, particularly following ifosfamide therapy, are increasingly being recognized in clinical practice (Table 21.2).

Cystinosis

Cystinosis is an autosomal recessive, multiorgan disorder that is characterized by intracellular deposition of cystine in numerous tissues. The first case resembling the description of nephropathic cystinosis was reported by Abderhalden in 1903.[27] Although confused by early investigators to be a variant of cystinuria, Bickel meticulously demonstrated cystinosis to be a cystine storage disease.[28]

Genetics

Cystinosis occurs in about 1: 150 000 live births worldwide, but may be considerably higher due to 'founder effects' in certain populations, such as French Canadians.[29] Cystinosis is caused by mutations in the *CTNS* gene that encodes cystinosin, a cystine transport channel protein in the lysosomal membrane.[30]

Pathophysiology

Lysosomes are the site of intracellular protein degradation and the constituent amino acids must exit this compartment for reuse in the cytoplasm. Although other amino acids exit freely through various channels, progressive cystine accumulation in lysosomes results from cystine-selective channel dysfunction.[31] Since the proximal tubule must reabsorb and catabolize the daily load of small-molecular-weight proteins present in the glomerular ultrafiltrate, the burden of cystine accumulation is particularly high in this nephron segment. Cystine accumulation eventually leads the affected cells to apoptotic death, and these events affect the proximal tubular cells much ahead of many other involved tissues.

Table 21.2 Causes of Fanconi syndrome (see also Table 20.2)

Idiopathic inherited Fanconi syndrome:
- Autosomal dominant
- Autosomal recessive
- X-linked variant

Inherited tubulopathies:
- Cystinosis
- Tyrosinemia
- Lowe syndrome
- Galactosemia
- Fructosemia
- Wilson disease
- Dent disease
- Mitochondrial disorders (cytochrome c oxidase deficiency)
- Fabry disease (glomerular involvement is also prominent)

Acquired tubulopathies:
- Ifosfamide therapy
- Cyclosporine therapy
- Cisplatin
- Heavy metal poisoning (lead)
- Glue sniffing

Clinical manifestations

Children with cystinosis usually present in the first year of life with manifestations of failure to thrive, polyuria, metabolic acidosis, hypokalemia, and hypophosphatemic, rickets (Figure 21.5). All races are affected, but Caucasian children with this disease frequently have fair complexion and blond hair compared with their parents. Although cystinosis is a systemic disease affecting almost all organ systems, renal dysfunction is the most prominent clinical manifestations in early years.

In the classical infantile form of the disease, cystine accumulation is demonstrable in amniocytes during gestation as well as in leukocytes at birth, but newborns may appear clinically well.[32] Unless there is an affected sibling, the diagnosis is often considered when infants are evaluated for growth failure,

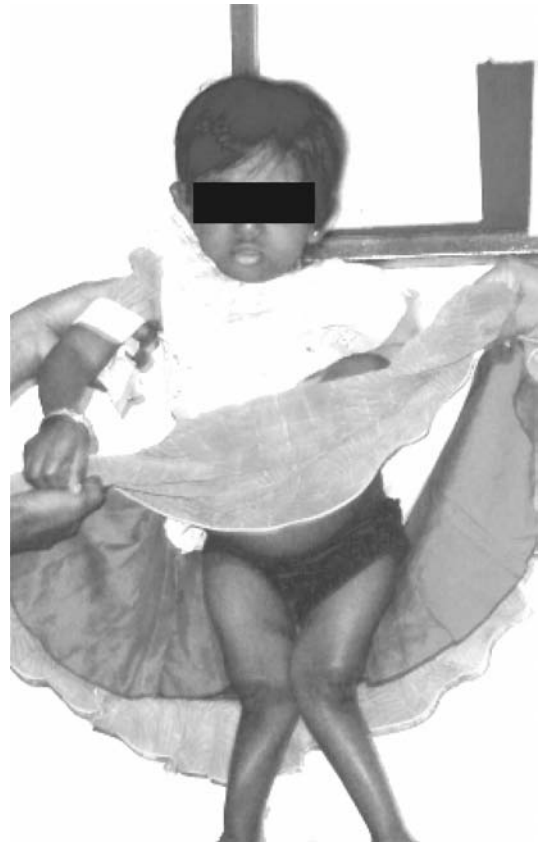

Figure 21.5 Photograph of a 10-year-old girl from India with untreated nephropathic cystinosis. Note the severe growth failure and rachitic deformities of the legs. The hair color was normal (black) in this patient, unlike the blond features usually seen in Caucasian patients.

rickets, or metabolic acidosis. Frequent episodes of dehydration, electrolyte abnormalities, and polyuria are other common manifestations at this age. Early in their clinical course, many of these young infants may be erroneously diagnosed as having Bartter syndrome, renal salt wasting, or diabetes insipidus. Corneal cystine crystal deposition (diagnosed by slit lamp examination) develops during the first year of life and the broad proximal tubular dysfunction also progresses during this time. A reasonable goal is to identify this disorder in the first year of life because of the positive impact of early cysteamine therapy on the progression of the disease.[32,33]

Growth failure, photophobia, and Fanconi syndrome are the dominant clinical manifestations during the first 5–6 years of life.[34] About 50% of cystinosis patients have hypothyroidism and photophobia by 5–10 years of age.[32] Glomerular dysfunction usually develops around 5 years of age, and progresses relentlessly to chronic renal failure and end-stage renal disease (ESRD). Renal insufficiency progresses in a linear fashion during the second half of the first decade and renal replacement therapy becomes necessary around 8–12 years of age in 95% of cases.[32] Between 6 and 12 years of age, glomerular proteinuria is seen in addition to the basal loss of low-molecular-weight proteins and is attributed to proximal tubular dysfunction. Serum protein level may decline with the onset of glomerular proteinuria. Despite severe aminoaciduria, cystine stones do not form in cystinosis because of polyuria and highly alkaline urine (due to proximal renal tubular acidosis). Cystine accumulation in bone may affect marrow function to some degree and lead to a much worse anemia than can be accounted for by renal insufficiency.

A less-severe form of cystinosis known as the 'juvenile' variant has also been reported. These patients have milder *CTNS* mutations and develop Fanconi syndrome and glomerular involvement during adolescence.[35,36] Growth failure is less conspicuous in these patients. Others may inherit a combination of a null and a very mild missense mutation causing corneal crystals and photophobia, without renal dysfunction (non-nephropathic cystinosis).[37]

Diagnosis

Diagnosis of cystinosis is suspected in a patient with growth failure, severe proximal tubular dysfunction, growth retardation, and hypophosphatemic rickets. An elevated leukocyte cystine level is diagnostic of cystinosis and can be performed in as little as 3 ml of heparinized blood. In homozygotes, the leukocyte cystine level ranges from 2 to 15 nmol half-cystine/mg of protein, compared with a normal value of <0.2 nmol half-cystine/mg of protein. Heterozygous carriers may be difficult to distinguish from normal controls.

Slit lamp examination reveals a characteristic cystine crystal deposition in the cornea in most children beyond the first few months of age. Hypothyroidism is common in patients with cystinosis, and thyroid function tests are necessary in all patients at initial presentation as well as in follow-up. Severity of Fanconi syndrome with metabolic acidosis, hypophosphatemia, generalized aminoaciduria, and glycosuria should be documented. Because of the risk of chronic kidney disease, renal function needs to be closely monitored, especially in children >5 years of age. Serial measurement of GFR, or 1/creatinine plots are helpful in predicting the time of onset of ESRD and the need for renal replacement therapy. Since renal disease is predictable in these patients, a diagnostic renal biopsy is seldom necessary. All biopsy tissues in these patients need to be handled in a special manner, so that cystine crystals are not washed away during tissue processing. Prenatal diagnosis of cystinosis has been available for over 30 years and is highly reliable. This test measures cystine in cultured amniocytes or cells obtained on chorionic villous sampling.[38]

Treatment

General Appropriate aggressive nutritional intervention should be initiated early, in order to avoid protein/calorie malnutrition resulting from vomiting and poor intake. In polyuric infants, additional fluid replacement is often necessary. Despite significant renal losses, replacement of organic solutes (amino acids, glucose, and low-molecular-weight proteins) is not warranted. The challenge in treating these infants lies in the individualization of the drug dosing schedules and amounts in order to assure tolerability of the therapy and avoid interference with normal food intake.

Metabolic acidosis Correction of metabolic acidosis requires massive (10–20 mEq/kg/day) oral alkali supplementation. Both sodium bicarbonate and citrate-based alkali therapy (Scholl's Solution, Bicitra) can be used to correct the metabolic acidosis. Bicitra provides 1 mEq of bicarbonate equivalent per ml. Potassium citrate-based alkali supplementation (PolyCitra) is often preferred, since it provides 2 mEq/ml of alkali equivalent and also helps to correct hypokalemia. Additional potassium chloride supplements may be necessary to correct hypokalemia.

Hypophosphatemia Oral phosphate therapy is essential in these patients in order to prevent hypophosphatemic rickets. Usual daily phosphate requirement (Neutraphos) is 25–75 mg/kg. Oral phosphate supplementation may bind dietary calcium and lead to hypocalcemia. In order to prevent this, and to enhance gastrointestinal phosphate absorption, calcitriol (10–30 ng/kg/day) should also be provided. It is prudent to monitor parathyroid hormone levels to optimize calcitriol dose.

Hyponatremia Since bulk reabsorption of sodium is prominently accomplished in the proximal tubule, mild hyponatremia is often seen in patients with cystinosis. Sodium supplementation is often necessary for correction of hyponatremia, and this may help to improve somatic growth. Non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin (2 mg/kg/day) as adjunctive therapy to reduce GFR and the filtered load, should be considered for infants who cannot maintain adequate solute balance. Such a therapy should be combined with drugs to protect the gastric mucosa.

Hypothyroidism Supplementation of levothyroxine to correct hypothyroidism should be initiated early in order to prevent clinical disease and growth retardation.

Cysteamine therapy In 1976, Thoene et al first reported the use of cysteamine to treat intralysosomal cystine accumulation in this disease.[39] A dose of 1.3–1.9 g/1.73 m^2/day (in four divided doses) rapidly reduces the level of leukocyte cystine to a 6-hour trough of 10–15% of untreated subjects.[33] Several long-term studies indicate that early oral cysteamine substantially delays progression of renal failure.[39–44] Similar benefits may be obtained for other tissues, such as the thyroid gland, muscles, and brain.[43] Photophobia is less responsive to oral cysteamine but is ameliorated by frequent (4–6 times/day) topical application of cysteamine eyedrops.[44]

Cysteamine's sulfurous odor and taste make long-term compliance difficult to achieve, and periodic monitoring of leukocyte cystine level may be helpful. When therapy is introduced after 2 years of age or if compliance is poor, renal failure may not be delayed, and is heralded by an increasing nephrotic-range proteinuria.

Renal transplantation is successful, since cystine accumulation does not occur in the genetically normal allograft. Despite proteinuria and polyuria from native kidneys, preemptive transplantation with living-related donor grafts is highly successful and there is no increased risk of graft thrombosis.[45] Once renal transplantation has been achieved, patient survival is determined by the ravages of cystinosis on other organs. Severe dysphagia, diabetes mellitus, and neurologic symptoms are particularly important. Whereas it may be impractical to continue cysteamine therapy during the early transplant period, it is prudent to reintroduce therapy as soon as is practical.

Dent disease

Children with Dent disease may also present with broad proximal tubular dysfunction. Affected children manifest hypercalciuric nephrolithiasis, hypophosphatemic rickets, and asymptomatic low-molecular-weight proteinuria.

This uncommon autosomal dominant disease is caused by inactivating mutations of the chloride channel (CLCN5) expressed in the luminal membrane of proximal tubular cells, thick ascending limb of the loop of Henle, and acid-secreting α-intercalated cells of the collecting duct.[46–48] The CLCN5 channel is intimately involved in the reabsorption of low-molecular-weight proteins from tubular fluid via endocytosis. Absence of the channel interferes with normal acidification of endosomes required for transfer of the adsorbed proteins to lysosomes and recycling of membrane fragments to the cell surface.[49] It is speculated that failure to degrade the internalized parathyroid hormone (PTH)/receptor complex allows sustained signaling that leads to excessive vitamin D activation and excessive calcium reabsorption from the intestine (Figure 21.6).[50] This postulate may explain the prominent manifestations of hypercalciuria, calcium stones, and nephrocalcinosis, which are characteristic of this disorder (Figure 21.7).[51]

The Fanconi syndrome in Dent disease is not as profound as that seen in cystinosis. Hypokalemia, metabolic acidosis, and hypophosphatemic rickets are also not uniformly present. An interesting feature pointed out by N Goldraich (pers comm) is that uptake of DMSA by the proximal tubular is strikingly reduced before significant loss of GFR is evident.[52] Progressive

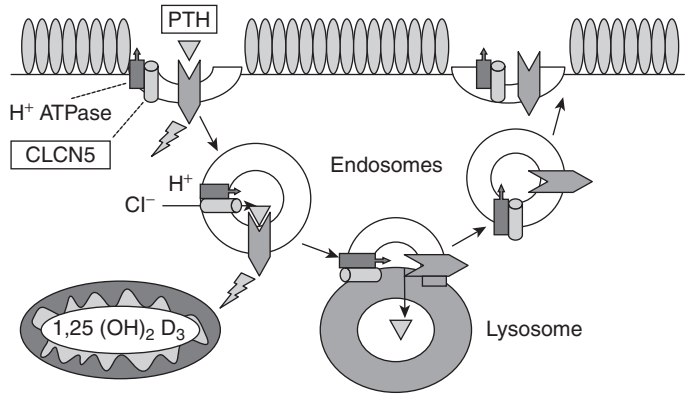

Figure 21.6 Schematic representation of the pathogenesis of Dent disease. Dent disease is caused by mutations of the chloride channel (CLCN5) at the luminal membrane of renal proximal tubules. This transporter is essential for reabsorption of the filtered low-molecular-weight proteins and electroneutral transport of hydrogen ions. These proteins are reabsorbed from the tubular lumen by endocytosis. During this process, acidification of the endosome is required for delivery of protein cargo to the lysosome for degradation prior to recycling normal membrane components to the cell surface. Defective CLCN5 function is thought to block this cycle, depleting the brush border membrane of normal transport proteins and allowing sustained signaling of receptor-bound parathyroid hormone (PTH).

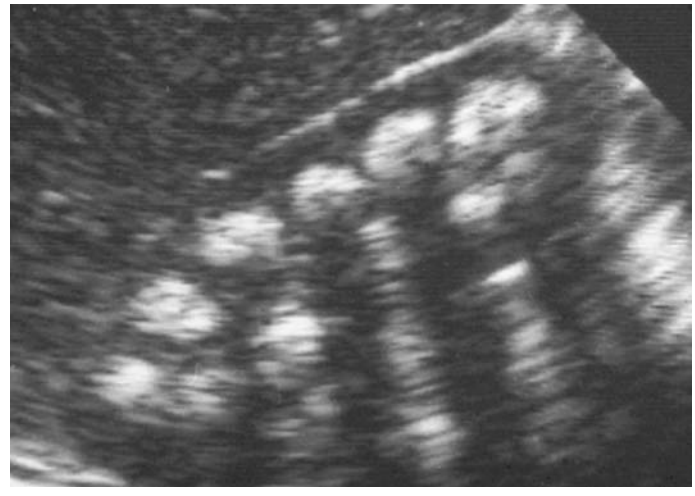

Figure 21.7 Renal ultrasound demonstrating nephrocalcinosis in a patient with Dent disease.

renal failure becomes evident in the second to third decade. Renal biopsies in the early course of the disease show nephrocalcinosis and glomerulosclerosis.[53] An optimal treatment for Dent disease is unclear. Hydrochlorothiazide therapy to diminish hypercalciuria and nephrocalcinosis, or strategies to reduce oral calcium absorption are logical.

Miscellaneous causes of Fanconi syndrome

Fanconi syndrome has been described with numerous other metabolic diseases (Table 21.2 and 20.2), including Lowe syndrome, Wilson disease, tyrosinemia, galactosemia, and fructosemia. Of special note are the mitochondrial cytopathies, which interfere with intracellular energy metabolism necessary for active renal tubular cell transport. In these disorders, Fanconi syndrome may be an early sign of the molecular defect involving the respiratory chain.[54] Severely affected infants may present in the newborn period with failure to thrive, lactic acidosis, and polyuria. Nearly half of the patients die within the first year of life, whereas some have progressive renal failure.[55,56] More than 80% of patients come to medical attention by the age of 2 years.[57] Moderate to severe proximal tubular dysfunction and lactic acidosis are often accompanied by protean neuromuscular symptoms. Renal biopsy may reveal glomerulosclerosis or diffuse interstitial nephritis giant mitochondria with paracrystalline inclusions on electron microscopy.

Whereas these defects sometimes involve mutations of the mitochondrial genome, it is important to note that 80% of respiratory chain genes are nuclear, and typical autosomal recessive inheritance is observed. Although a precise molecular diagnosis is often elusive, the defect may be evident by studies of oxidative metabolism in cultured skin fibroblasts or on cytochrome c oxidase staining of muscle biopsies. Although strategies to bypass defective portions of the respiratory chain have been tried, there is no satisfactory therapy for mitochondrial cytopathies.[57]

Defective salt reabsorption in the distal nephron

Children with inherited forms of isolated renal salt wasting present early in life with polyuria and failure to thrive. However, the age at which they come to medical attention is largely dependent on the renal tubular segment involved and the severity of solute loss. Although much of the filtered salt load is reabsorbed in the proximal tubules, the final determinants of sodium excretion are luminal transporters positioned along the thick ascending limb of Henle (NKCC2), the distal convoluted tubule and connecting segment (NCC and ENaC), and the collecting duct (ENaC). Dysfunction of each of these transporters is specifically inhibited by a different class of diuretic drugs and corresponds to one of the distinct syndromes of renal salt wasting (Table 21.3).

Bartter syndrome

Frederic Bartter first described this autosomal recessive syndrome characterized by growth failure, metabolic alkalosis, juxtaglomerular apparatus cell hyperplasia, hyperreninemia, and lack of hypertension.[58] This disorder is caused by dysfunction of Na/K/Cl cotransport (Figure 21.8) in the thick ascending limb of Henle (TALH). The syndrome is mimicked by sustained furosemide administration, which directly inhibits the luminal NKCC2 transporter, itself. As a result of the profound lack of sodium, chloride, and water reabsorption in the TALH, more distal sites of sodium absorption are overwhelmed. This results in high urinary volume, reaching 4–8 L/m^2/day. Salt losses cause volume contraction and elicit a number of characteristic compensatory responses, including hyperreninemia (10–20 times the upper limit of normal), with striking hypertrophy of the juxtaglomerular apparatus and excessive production of renal prostaglandin E_2. Secondary hyperaldosteronism stimulates sodium reabsorption in the collecting duct and salvages some of the salt, which escapes the TALH, but also results in a chronic alkalosis, and enhances renal potassium wasting.

Failure of the Na/K/Cl cotransporter in the TALH also makes it impossible to generate a positive potential in the tubular lumen, eliminating the driving force for calcium reabsorption. Thus, patients with severe forms of Bartter syndrome exhibit hypercalciuria and nephrocalcinosis. Polyuria in Bartter syndrome can sometimes resemble nephrogenic diabetes insipidus, but urine osmolarity is usually >100 mOsm/L in the untreated state, and 1-desamino-8-D-arginine vasopressin (DDAVP) infusion (0.3 μg/kg) inhibits free water clearance.[59]

Neonatal Bartter syndrome

In the neonatal form of Bartter syndrome, there is usually a history of third trimester polyhydramnios and premature birth.[60] Affected infants may rapidly become dehydrated with profound hyponatremia and hypokalemia, making early recognition of the syndrome lifesaving. As predicted, some affected neonates (type 1 Bartter syndrome) were found to have inactivating mutations of the Na/K/Cl_2 cotransporter gene (*SLC2A1*).[61] However, a second genetic type of neonatal Bartter syndrome (type II) has been identified that is associated with mutations of the gene (*KCNJ1*) encoding an outwardly rectifying potassium channel (ROMK) in the thick ascending limb of Henle.[62] The latter channel normally allows recycling of potassium ions to the tubular fluid and is essential for sustained function of the Na/K/Cl_2 cotransporter. Interestingly, ROMK is also needed for potassium secretion in the collecting duct, so hypokalemia is not as profound as in neonates with mutations of *SLC2A1*. In the neonatal period some infants may even be slightly hyperkalemic.

Classic Bartter syndrome

In slightly milder forms of Bartter syndrome, children may present during the first 2 years of life with polyuria, vomiting, episodes of unexplained fever, and growth retardation.[63] Among these patients, a third genetic type of Bartter syndrome has

Table 21.3 Syndromes of abnormal renal tubular salt transport[a]

Syndrome	Affected solute	Transporter	Nephron segment	Inhibitor	Clinical characteristics
Bartter syndrome	Na/K/Cl	NKCC2	TALH	Furosemide	Neonatal and early presentation, severe salt wasting and polyhydramnios common
	K^+	ROMK	TALH CCD		Hypokalemia is less pronounced
	Cl^-	ClC-Kb	TALH DCT/CCT		Classic Bartter syndrome, salt wasting is modest
	Cl^-	Barttin	TALH Thin LH Cochlea		Early and neonatal presentation, salt wasting is severe, sensorineural deafness
Gitelman syndrome	Na/Cl	NCCT	DCT	Thiazides	Hypocalciuria and hypomagnesemia, metabolic alkalosis, growth failure less likely, neuromuscular symptoms dominate. Poyhydramnios less likely
	Na/Cl	NCCT (WNK1/WNK4)	DCT		
PHA1	Na Na	ENaC MR	DCT/CCT DCT/CCT	Amiloride	Neonatal presentation, hyponatremia, hyperkalemia
Gordon syndrome	Na/Cl	NCCT	DCT	Thiazides	Hypertension, acidosis, hyperkalemia, low renin
Liddle syndrome	Na	ENaC	DCT/CCT	Amiloride	Hypertension, alkalosis, hypokalemia, low renin
AME	Na	ENaC (11β-HSD)	DCT/CCT		Hypertension, low birth weight, hypokalemia, low renin, hypercalciuria, nephrocalcinosis, consanguinity common
	Na	ENaC	DCT/CCT		

[a]For each syndrome, the specific tubular transport system (or transporter component) involved and its associated inhibitor (diuretic agent) are indicated. For abbreviations see text.

PHA, primary hyperaldosteronism; AME, apparent mineralocorticoid excess; TALH, thick ascending loop of Henle; CCD, cortical collecting duct; OCT, distal collecting duct; LH, loop of Henle; CCT, Cortical collecting tubule.

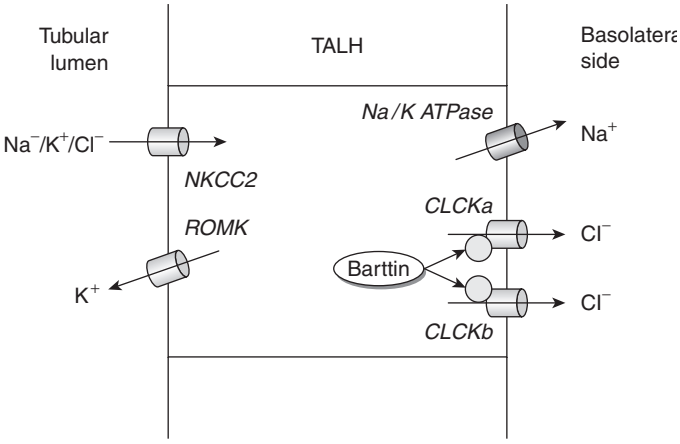

Figure 21.8 Schematic representation of a cell from the thick ascending limb of the loop of Henle (TALH), showing transport systems involved in the pathogenesis of Bartter syndrome. Na and K are normally reabsorbed along with two chloride ions by the furosemide-sensitive cotransporter at the luminal surface. Recycling of KCl to the tubular lumen (via ROMK) is essential to prime NKCC2 function. At the basolateral surface, chloride exits via two channels (CLC-Ka and CLC-Kb) which share a common subunit (barttin). Sodium is pumped across the basolateral membrane via the Na/K ATPase. Type I Bartter syndrome results from a defect in the NKCC2 channel, type II disorders results from defective ROMK channel, type III disorder is caused by defects in the CLC-Kb channel, and type IV disorder is the result of mutation in barttin, a critical protein comprising CLK-a and CLK-b channels. The net impact of these derangements in Bartter syndrome is inability to reabsorb sodium and chloride in the TAHL. Renal salt and water loss results in activation of the renin–angiotensin system and stimulation of sodium reabsorption in the collecting duct – in exchange for secreted hydrogen ion or potassium – resulting in hypokalemia and metabolic alkalosis.

been identified. Affected children bear homozygous mutations of a chloride channel gene (*CLCNKB*) expressed in the TALH, the distal convoluted tubule, and in α-intercalated cells of the cortical collecting duct (type III).[64] The CLC-Kb serves basolateral efflux of chloride, reabsorbed along with sodium and potassium by the $Na/K/Cl_2$ cotransporter of the TALH. However, the presence of a second chloride channel (CLC-Ka) permits some chloride efflux, so salt wasting is only moderately severe and patients tend not to have hypercalciuria and nephrocalcinosis.[65]

Type IV Bartter syndrome is caused by mutations of the *BSND* gene, encoding the protein barttin, expressed in basolateral membrane of TALH cells, intercalated cells of the collecting duct, and in cells of the cochlea and vestibular system.[66] Barttin is a critical subunit of both the CLC-Ka and CLC-Kb chloride channels in the TALH. Patients with null mutations present with severe salt wasting during the neonatal period. On the other hand, patients with mild Barttin mutations may not present until adulthood.[67] As in type III Bartter syndrome, hypercalciuria and nephrocalcinosis are uncommon. Since CLC-Ka is expressed in the ear, type IV Bartter patients develop deafness.[68]

Finally, it has been noted that patients with activating mutations of the calcium-sensing receptor may exhibit modest salt wasting and hypokalemia.[69] Since the disease is characterized by autosomal dominant hypocalcemia, it is easily distinguished from Bartter syndrome. The mechanisms for salt wasting in the two conditions are related. Increased reabsorption of calcium produces a less favorable electrical gradient for the NKCC2-mediated salt reabsorption in the TALH.

Treatment

Treatment of Bartter syndrome focuses on adequate sodium, chloride, and potassium replacement. Use of NSAIDS to block the effects of prostaglandins on the kidney is also helpful. During infancy, the salt content of milk or formula can be adjusted to 40–50 mEq/L. Oral potassium chloride (5–10 mEq/kg/day in four divided doses) may be necessary in order to correct hypokalemia, but is not always well tolerated. Traditionally, indomethacin (2–3 mg/kg/day in divided doses) has been used. However, with long-term use, this may cause significant gastrointestinal complications. Vaisbich et al reported that nearly 50% of their patients developed gastrointestinal toxicities, ranging from gastritis with vomiting to perforated gastric ulcer.[70] The same preliminary report suggests that selective cyclooxygenase-2 (COX-2) inhibitors can be highly effective and could accrue the benefit of reduced gastrointestinal toxicity with prolonged use.[70] In most Bartter syndrome patients, GFR is normal when volume is restored, but progressive renal failure may be noted in a small proportion of patients during childhood. It is unclear whether this is a complication of the disease itself or renal sensitivity to chronic therapy with indomethacin.[71]

Gitelman syndrome

Gitelman syndrome is an autosomal recessive disorder characterized by metabolic alkalosis, hypokalemia, hypocalciuria, hypomagnesemia, hyperreninemia, and a lack of hypertension.[72] Although Gitelman syndrome resembles Bartter syndrome in some of its manifestations, it is a relatively mild clinical disorder, and hypocalciuria and hypomagnesemia are two important biochemical markers of this disorder. Gitelman syndrome is caused by mutations of the *SLC12A3* gene, which encodes the Na/Cl cotransporter (NCCT) in the distal convoluted tubule.[73,74]

Clinical manifestations

Although children with Gitelman syndrome have been described, this disorder has been most commonly reported in adolescents and adults. Parents are without disease manifestation, but an occasional affected sibling may be seen in the same family. Consanguinity has not been reported in these patients. Many affected adults are asymptomatic and the diagnosis of the disorder is often made during investigation of hypokalemia. Those presenting in childhood do not usually have a history of polyhydramnios, or low birth weight, and growth retardation is also a less prominent feature than in patients with Bartter syndrome.[72,75] Common manifestations of Gitelman syndrome are neuromuscular symptoms such as paresthesias, tingling,

tetany, and muscle cramps that result from hypomagnesemia. Seizures due to hypomagnesemia and consequent hypocalcemia are rare but can be the initial manifestations in some patients.[76] Salt craving, non-specific symptoms of fatigue, and difficulty in concentrating are also reported as symptoms by adults with Gitelman syndrome.[76] Although renal salt wasting in Gitelman syndrome is mild in most patients, other patients may manifest sodium loss comparable to that seen in mild Bartter syndrome. Prolonged QT interval on electrocardiograms and potential risk of cardiac arrhythmias have been recently recognized in these patients.[77]

Pathophysiology

Gitelman syndrome results from a defect in the Na/Cl cotransporter and impaired salt transport in the distal convoluted tubule (Figure 21.9). Since NCCT is the target of thiazide diuretics, manifestations of Gitelman syndrome are mimicked by chronic thiazide administration. Only about 5–10% of the filtered salt load is reabsorbed in the distal convoluted tubule and compensatory responses of the TALH and the collecting tubule can nearly compensate for this deficit. Thus, patients suffering from Gitelman syndrome exhibit only mild renal salt wasting, and the increase in plasma renin level is also modest. Downstream compensatory sodium and chloride reabsorption in the collecting duct, under the influence of increased aldosterone, drives potassium secretion in this nephron segment, accounting for marked hypokalemia.

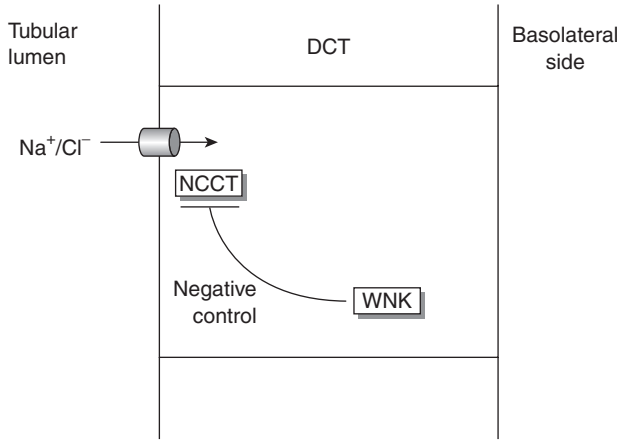

Figure 21.9 Schematic representation of a cell from the distal convoluted renal tubule (DCT) showing the pathogenesis of Gitelman syndrome. The Na/Cl cotransporter (NCCT) at the luminal membrane facilitates reabsorption of sodium and chloride in this nephron segment. Inactivating mutations of NCCT cause failure of this transport and result in Gitelman syndrome. WNK (with no kinase) proteins negatively regulate the NCCT channel. *WNK* gene mutations that result in constitutive inactivation of the NCCT transporter lead to defective salt reabsorption in the DCT and development of Gitelman syndrome. Gordon syndrome is an exactly opposite disorder, with mutations in WNK proteins that result in loss of negative control over the NCCT channel. Excessive sodium and chloride reabsorption in the DCT results in hypervolemia and hypertension.

Since the TALH is intact in patients with Gitelman syndrome, compensatory salt reabsorption in this nephron segment enhances the luminal electropositive potential and promotes secondary calcium reabsorption. The resultant hypocalciuria is an important clue distinguishing Gitelman syndrome from Bartter syndrome.[75,78] Like patients treated with thiazide diuretics, Gitelman patients may have increased bone density.[79]

The mechanism causing hypomagnesemia in Gitelman syndrome is still not well understood, especially since only 5–10% of filtered magnesium is reabsorbed in the distal convoluted tubule. Nevertheless, sustained hypomagnesemia blunts parathyroid hormone release and compromises the function of enzymes such as alkaline phosphatase that regulate pyrophosphate concentration in the extracellular space. The latter effect may explain the pathogenesis for chondrocalcinosis seen in Gitelman syndrome.[80]

Treatment

Salt wasting is usually mild in Gitelman syndrome and NSAID therapy is not usually required. Hypokalemia can often be corrected with oral potassium supplements (2–3 mEq/kg/day), but some patients may also require the potassium-sparing diuretics, such as amiloride or spironolactone. Since the disease centers on dysfunction of the Na/Cl cotransporter (NCCT), salt supplements would seem to be logical, but downstream delivery of sodium to the collecting duct may worsen renal potassium wasting, unless used in combination with a potassium-sparing diuretic. Oral magnesium supplements (discussed in Chapter 3) may be essential to prevent muscle cramping. Correction of hypomagnesemia may diminish the impact of renal potassium wasting and correct functional hypoparathyroidism.[81]

Pseudohypoaldosteronism

This rare syndrome is characterized by renal salt wasting, hyperkalemia, and metabolic acidosis, despite markedly elevated levels of renin and aldosterone.[82] Affected infants present in the first weeks of life with dehydration and hyponatremia. Two clinically distinct forms of pseudohypoaldosterone (PHA1) have been identified. PHA1 can be inherited as an autosomal recessive or an autosomal dominant disorder. The autosomal recessive form of PHA1 is caused by homozygous loss of one of either the α, β, or γ subunit of the luminal sodium channel (ENaC) in the cortical collecting tubule (Figure 21.10).[83,84] Dysfunction of the ENaC blocks sodium reabsorption, but also eliminates the driving force for secretion of potassium and hydrogen ions in the cortical collecting tubule. Since ENaC expression is normally stimulated by aldosterone, the features of this syndrome are mimicked by spironolactone. Distribution of ENaC is not restricted to the kidney and affected infants also have severe salt wasting in the colon, sweat glands, and salivary glands and this disorder may superficially resemble cystic fibrosis. But the two disorders are distinguished by the absence of acidosis and hyperkalemia in cystic fibrosis. Children with

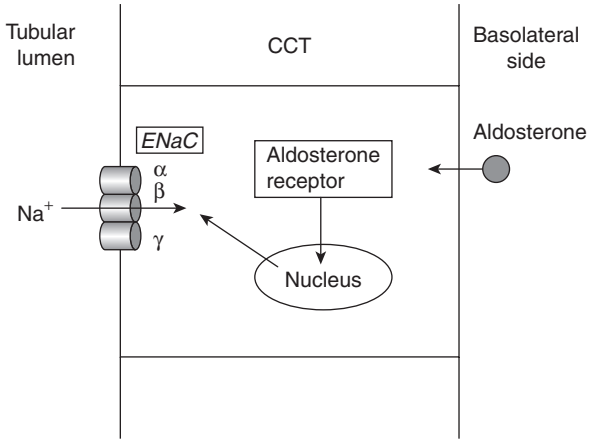

Figure 21.10 Schematic representation of a cell from the cortical collecting tubule (CCT) showing pathogenesis of pseudohypoaldosteronism type 1 and Liddle syndrome. Subunits of the sodium channel (ENaC) at the luminal membrane (α, β, γ) are also shown. Aldosterone binds to the mineralocorticoid receptor within the nucleus, resulting in stimulation of genes that enhance the activity of the ENaC. Inactivating mutations of the *ENaC* subunit genes result in pseudohypoaldosteronism type 1, whereas mutations causing constitutive hyperfunction of the transporter result in Liddle syndrome.

PHA1 have recurrent episodes of salt wasting and hyperkalemia, requiring therapy with oral salt supplements, sodium bicarbonate, and potassium exchange resins (Kayexalate) for life.

An autosomal dominant form of PHA1 caused by heterozygous loss of the mineralocorticoid receptor gene has also been described.[85,86] Although affected neonates may be extremely ill and can die from hyperkalemia, they respond well to oral salt supplementation. With volume expansion and adequate delivery of sodium to the collecting tubule, hyperkalemia can be controlled. With tubular maturation, the clinical problems resolve by 1–2 years of age, and heterozygous adults remain asymptomatic. Aldosterone level stays elevated (>30 ng/dl), apparently compensating for the reduced number of mineralocorticoid receptors.

Disorders of excessive tubular salt absorption and hypertension

Liddle syndrome

This autosomal dominant condition is the prototype of several hereditary forms of hypertension in which inappropriate reabsorption of salt by the renal tubule causes subtle volume expansion and hypertension. Liddle syndrome is characterized by hypertension manifesting during childhood, metabolic alkalosis and hypokalemia in the setting of low urine sodium excretion, and high urinary potassium excretion.[87] Whereas the clinical picture resembles hyperaldosteronism, plasma renin and aldosterone levels are actually low due to intravascular volume expansion. Thus, the urinary aldosterone-to-potassium ratio is typically about 15% of normal.[88] The syndrome is caused by mutations of either the β or γ subunit of the epithelial sodium channel (ENaC) in the cortical collecting tubule (see Figure 21.10) which alter its turnover and lead to increased channel abundance at the luminal membrane.[89,90] Not all cases of Liddle syndrome result from ENaC mutations. A similar autosomal dominant syndrome due to gain-of-function mutations in the mineralocorticoid receptor has been reported in one family.[85] Although the clinical features were identical to Liddle syndrome, an unusual characteristic was the worsening of hypertension during pregnancy.

Therapy of Liddle syndrome consists of salt restriction and use of amiloride, which specifically inhibits the ENaC channel. Amiloride in a dose of 20 mg/1.73 m^2/day is usually adequate for blood pressure control. Thiazides and triamterene can also provide control of hypertension and hypokalemia, but spironolactone is ineffective.[91] Renal transplantation done in a patient with Liddle syndrome was able to cure hypertension.[91]

Glucocorticoid-remediable aldosteronism

Glucocorticoid-remediable aldosteronism (GRA) is a rare autosomal dominant disorder present with hypertension, low plasma renin, and intermittently elevated plasma aldosterone levels.[92] The distinguishing feature of this disease is the paradoxical increase in blood pressure overnight and the rapid control of blood pressure induced by treatment with physiologic doses of glucocorticoids. Serum bicarbonate and potassium are generally in the normal range.

In normal individuals, aldosterone is produced in the zona glomerulosa of the adrenal cortex, under the influence of aldosterone. In GRA, excessive aldosterone production occurs in the adrenal under the sole control of adrenocorticotropic hormone (ACTH). These patients have a genetic recombination event with the formation of a chimeric gene in which ACTH-responsive promoter of 11β-hydroxylase gene (*CYP11B1*) and aldosterone synthase gene (*CYP11B2*) fuse together.[93] As a consequence, ectopic expression of aldosterone synthase in the adrenal cortex (zona fasciculata) results in increased aldosterone synthesis that is under the regulatory control of ACTH.

The clinical diagnosis is suspected in a patient with strong family history of GRA, hypertension, low plasma renin level, and hypokalemia. Although GRA has been reported in young children and even neonates, most children with this disorder present with hypertension by 13 years of age.[94,95] The degree of hypertension can, however, be variable, and may range from mild elevation of the blood pressure to severe hypertension. Suppressed plasma renin level, and hypokalemia in a hypertensive patient should prompt consideration of GRA as a possible cause.

Diagnosis of GRA can now be established by a test for detecting the chimeric GRA gene. The test, using the Southern blot method, is highly reliable, with a reported sensitivity of 92%

and a specificity of 100%. It is not yet available commercially, but can be requested through the International GRA Registry (http://www.brighamandwomens.org/gra/). A rapid test for use on cord blood for early diagnosis in neonates at risk of the disease has been proposed.[96] Traditionally, GRA has been diagnosed by demonstrating suppression of plasma aldosterone to <4 ng/dl, or reduction of plasma aldosterone level to ≤80% compared with baseline following a 2–4 day dexamethasone test therapy (dexamethasone suppression test).[97] Other metabolc markers of GRA are 18-hydroxycortisol and 18-oxocortisol, and both can be elevated to >20 times normal value for age in the 24 hour urine samples. The ratio of urinary tetrahydro-18-oxocortisol to aldosterone is often >2.0 (normal=0.2).[94]

Treatment of GHA is achieved by suppression of ACTH by the use of exogenous glucocorticoids. In children, Dluhy et al reported that daily use of dexamethasone 0.5 mg, or hydrocortisone 6.5–15 mg, was sufficient to result in adequate control of hypertension.[97] Equivalent doses of prednisone can also be used. Excessive steroid dose should be avoided, since iatrogenic Cushing's syndrome and poor linear growth can occur in children. The goal of steroid therapy is to achieve an adequate blood pressure control and not normalization of aldosterone or other biochemical markers of the disease, since these remain elevated despite adequate therapy. Other recommended adjunctive therapies include spironolactone and amiloride. Non-directed pharmacotherapy with angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers does not provide adequate blood pressure control.[95]

Gordon syndrome

Gordon syndrome is another familial form of autosomal dominant hypertension in which hyperkalemia and acidosis resemble aldosterone deficiency, plasma renin is paradoxically low, and there is excessive tubular reabsorption of sodium.[98] The hallmark of this syndrome is responsiveness to thiazide therapy. Affected children may present with hypertension in the neonatal period, but some cases have been identified only in their teens or in adult life. Adults may develop periodic episodes of paralysis, whereas hypertension and hyperkalemia are often severe.[99]

Gordon syndrome is genetically heterogeneous and may be caused by mutations of the *Wnk1* or *Wnk4* genes, which are expressed in the distal convoluted tubule and collecting duct (see Figure 21.9) and appear to exert complex control over the sodium chloride cotransporter (NCCT).[100] All features of this syndrome respond to treatment with hydrochlorothiazide 1–2 mg/kg/day.

Syndrome of apparent mineralocorticoid excess

The syndrome of apparent mineralocorticoid excess (AME) is an autosomal recessive disease characterized by low birth weight, suboptimal somatic development, and onset of hypertension in early childhood.[101] Consanguinity or endogamy is common. This syndrome is caused by homozygous mutations of 11β-hydroxylase dehydrogenase, which normally inactivates circulating cortisol in the kidney, preventing its mineralocorticoid effects on tubular transport.[102,103]

Patients may have polyuria due to hypokalemic nephropathy and acquired nephrogenic diabetes insipidus. Excessive sodium/potassium exchange in the cortical collecting tubule resembles hyperaldosteronism, but plasma renin and aldosterone levels are suppressed. Hypercalciuria and nephrocalcinosis are also common. Secondary target organ damage due to hypertension, such as concentric left ventricular hypertrophy and retinopathy of hypertension, are common.

Diagnosis of AME should be suspected in a patient with hypertension, metabolic alkalosis, hyporeninemia, and almost undetectable levels of aldosterone. Whereas consanguinity may be present in the families, family history of the same disorder is usually sparse, unlike in patients with GRA. Biochemical confirmation of the diagnosis is achieved by assaying the ratio of urinary excretion of cortisol to cortisone. These metabolites are assayed as tetrahydrocortisol (THF), allotetrahydrocortisol (5αTHF), and tetrahydrocortisone (THE). The ratio of (THF+5αTHF)/THE is elevated several-fold in patients with AME (range 6–33 times the normal value of <1).[101] Assaying the *HSD11B2* gene, which codes for 11β-hydroxysteroid dehydrogenase, is now available commercially, and provides the confirmation of the diagnosis of AME.

Early aggressive treatment of the syndrome with spironolactone is important to avert the dangerous swings in blood pressure associated with cardiovascular complications.[104] The dose of spironolactone necessary for adequate blood pressure control can range from 2 to 10 mg/kg/day. Thiazides may be added to reduce hypercalciuria as well as to achieve a reduction in spironolactone dose. Hypokalemia should be corrected by supplementation of oral potassium compounds. Renal transplantation is curative.[104]

Disorders of tubular magnesium reabsorption

Several familial disorders of renal magnesium reabsorption have been described. Affected infants may present early in life with tetanic convulsions or may come to medical attention because of episodic muscle cramping later in life. Seizures are initially treated with intravenous calcium and magnesium. Subsequently, oral magnesium supplements (e.g. magnesium glucoheptonate 0.42 mmol/ml) are gradually increased until serum magnesium levels can be maintained above 0.5 mmol/L. The effective dose of magnesium is highly variable and depends both on the nature of the magnesium transport defect and on the intestinal response. In some children, high doses of oral magnesium may induce diarrhea before serum levels can be normalized, so that intermittent parenteral magnesium is required.

Familial hypomagnesemia with hypercalciuria

The disorder known as familial hypomagnesemia with hypercalciuria (FHH) is an autosomal recessive disorder that is characterized by renal magnesium and calcium wasting in the TALH. Hypomagnesemia and hypocalcemia result in muscle spasms, seizures, paresthesias, and muscle weakness. Hypercalciuria predisposes to urinary tract stones, and children may present with hematuria in the first years of life.[105] Progressive renal failure has been described[106] and many reach end-stage renal failure during the teenage years.[105] Calcification of basal ganglia, cornea, and joints suggest an abnormality affecting soft tissue calcium deposition. PTH levels are elevated in this disorder, despite low serum magnesium. Male infertility is common.

FHH is caused by mutations of the paracellin-1 gene located on the long arm of chromosome 3 (3q27).[105] Paracellin-1 is normally expressed at the tight junctions between cells of the TALH. Since magnesium reabsorption occurs via the paracellular pathway, paracellin-1 is believed to be an integral part of the membrane complex regulating divalent cation reabsorption. Unfortunately, magnesium replacement or thiazide therapy does not affect the progression of renal failure.[105]

Hypomagnesemia with severe hypocalcemia

Hypomagnesemia with severe hypocalcemia (HSH) is an autosomal recessive disorder that presents in the first 1–6 months of life with hypocalcemic seizures or tetany, and barely detectable levels of PTH.[107] Affected infants usually exhibit failure to thrive and may also have developmental delay. The disease is caused by homozygous mutations of the *TRPM6* gene encoding a cation channel protein expressed in the intestine and distal convoluted tubule of the kidney.[108–110] The combination of poor intestinal absorption and renal leak of magnesium depletes whole-body stores. Hypomagnesemia causes functional hypoparathyroidism and accounts for the striking hypocalcemia. Interestingly, the renal magnesium leak may be difficult to demonstrate at presentation. Although the fractional excretion of magnesium ranges from 3 to 5% in normal children, the kidney should usually reduce this to <1% in the face of hypomagnesemia. Once supplementation has brought serum magnesium to the lower limit of normal (0.6 mmol/L), renal magnesium wasting may then become evident.[110] The effective dose of oral magnesium supplements needed to normalize the serum magnesium level may range from 0.4 to 4 mmol/kg/day, and parenteral therapy is occasionally necessary.

Disorders of water reabsorption

Maintaining water balance is one of the chief regulatory functions of the renal tubules. Normal adult kidneys, with a GFR of 100 ml/min/1.73 m^2, produce about 144 L of glomerular ultrafiltrate daily [(100 ml × 60 min/h × 24 hours)/1000]: approximately 142.5 L of which is reabsorbed by the renal tubules in normal adults, leaving only 1.5 L to be excreted as urine. Tubular water reabsorption is driven by osmotic forces throughout the nephron, and follows tubular reabsorption of sodium. The 'countercurrent multiplier' system helps concentrate of the urine, and active reabsorption of water in the collecting ducts, under the influence of vasopressin, fine-tunes the final urinary concentration.

Vasopressin and aquaporins

Transport of water across biologic membranes has been debated for a long time. Serendipitous discovery of aquaporins (AQP), the water transport channels, by Agre and colleagues established the molecular mechanism of water reabsorption.[111] By now, at least 10 types of aquaporins (AQP 1–10) have been described in humans, and their distribution has been noted in diverse water-permeable tissues of the animal and plant kingdom. At least seven aquaporins are known to be present in various sites within the renal tissues.[112] Of these, AQP1, which was the first aquaporin to be described, is dominantly present in the proximal tubule and the thin descending limb of the loop of Henle. AQP2, on the other hand, is exclusively present in the distal collecting duct. Once synthesized by the tubular cells, aquaporins are signaled to reach the water transport sides of the tubular cell membrane. In these locations, aquaporins then act as selective water transport channels that conduct the osmotically driven water from the tubular lumen into the tubular cell and out of the cell on the basolateral aspect.[112] The mechanisms of aquaporin regulation in the tubular cells are the subject of ongoing and active investigations.

The antidiuretic hormone, or arginine vasopressin (AVP), is well known to regulate the urinary concentrating process by enhancing the permeability of water in the collecting duct. AVP is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus as a prehormone known as prepro-AVP. From its site of synthesis, the prepro-AVP moves along neuronal axons into the posterior pituitary attached to a carrier protein called neurophysin II (NPII). Within the posterior pituitary, the prepro-AVP is eventually converted to AVP and stored in the neurosecretory granules. AVP is released into the circulation in response to increased plasma tonicity, but other physiologic factors, such as pain, can also lead to the release of the hormone.

The mechanism of action of AVP on the collecting duct has been further elucidated in light of the discovery of aquaporins. In mediating its action on the collecting tubule cells, AVP binds to the AVP type 2 receptor (V2R), which is present on the basolateral aspect of these cells. This interaction initiates production of cyclic adenosine monophosphate (cAMP), which is used for phosphorylation of AQP2 stored in the intracellular vesicles, and their eventual incorporation on the luminal cell membrane.[112] The AQP2 then promotes water reabsorption from the tubular lumen (Figure 21.11).

Diabetes insipidus

Diabetes insipidus (DI) is characterized by a defect in renal water causing polyuria. In infants, this can result in recurrent

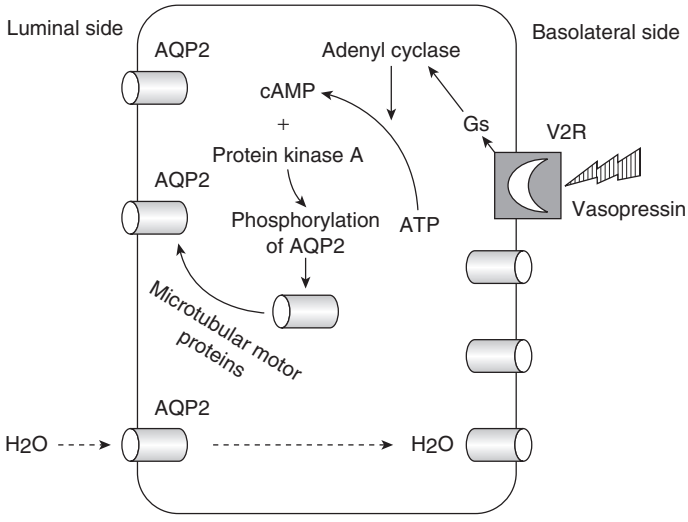

Figure 21.11 Pathophysiology of action of vasopressin and aquaporins (AQP) in water transport in the collecting duct. Vasopressin binds to the vasopressin receptor (V2R). Through the G proteins (Gs), this interaction leads to activation of adenylcyclase and formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP is used for phosphorylation of aquaporin 2 (AQP2), which is then moved from the vesicles to the cell membrane by microtubular motor proteins. Once incorporated into the cell membranes, AQP2 helps conduct water into the tubular cell from the luminal surface and out of the tubular cell (via AQP3) on the basolateral surface.

Table 21.4 Causes of diabetes insipidus in children

Central diabetes insipidus

1. Inherited:
   - Autosomal dominant
   - Autosomal recessive
2. Cerebral malformations (septo-optic dysplasia)
3. Acquired:
   - Trauma
   - Tumors and infiltrative lesions (craniopharyngioma, tuberculoma, histiocytosis X, sarcoid granuloma)
   - Infections (meningitis, encephalitis)
   - Hypoxic brain injury

Nephrogenic diabetes insipidus

1. Inherited:
   - X-linked recessive (*V2R* mutations)
   - Autosomal recessive (*AQP2* and *AQP1* mutations)
2. Acquired and secondary:
   - Postobstructive diuresis
   - Obstructive uropathy
   - Renal dysplasia
   - Sickle cell disease
   - Chronic kidney disease
   - Hypokalemic nephropathy
   - Hypercalcemia
   - Severe protein malnutrition
   - Drugs:
     Amphotericin B
     Tetracycline
     Lithium
     Diphenylhydantoin

episodes of dehydration and hypernatremia. DI can be caused by a deficit of AVP synthesis or release (central DI), or by inadequate renal response to the adequate AVP produced by the posterior pituitary (nephrogenic DI). Table 21.4 lists the causes of DI in children. This chapter will focus only on the description of nephrogenic DI.

Nephrogenic diabetes insipidus

Hereditary nephrogenic diabetes insipidus (NDI) is a rare disorder of vasopressin-stimulated water reabsorption via the luminal water channels in the cortical and medullary collecting ducts.[113] In Quebec, the incidence of NDI is estimated to be about 1 per 1 000 000.

Genetics

About 90% of the cases of NDI are X-linked and are caused by mutations of the *V2R* gene encoding the vasopressin receptor.[114,115] Over 150 distinct mutations have been described worldwide, but significant founder effects are well known.[119] Typical of X-linked recessive diseases, female NDI carriers are generally asymptomatic, or report only modest polydipsia. However, an occasional female with *V2R* mutation develops clinical features approaching those of affected males. About 10% of NDI cases are autosomal recessive and are due to homozygous mutations of the *AQP2* gene encoding the aquaporin protein that forms water channels in the luminal membrane of collecting duct cells in response to vasopressin stimulation.[117] The clinical manifestations of these patients are identical to those in males with X-linked *V2R* mutations. One family with a missense mutation of the *AQP2* gene transmitted a mild form of NDI in an autosomal dominant fashion.[118] This particular aquaporin mutation seems to trap the normal water channel in an intracellular position. A very mild form of NDI has been ascribed to mutations of *AQP1*, mediating water flux in the proximal tubule.[119] These patients have a modest inability to concentrate the urine maximally in response to water deprivation.

Clinical manifestations

Most children with NDI are discovered within the first year of life. Median age at presentation in one large study was 9 months.[116] Family history of NDI may lead to early diagnosis in the neonatal period in some. Interestingly, polyhydramnios is less evident in NDI than in Bartter syndrome,[113] and affected newborns are relatively protected from dehydration during the first few days because of low GFR. However, by the end of the first week of life, massive polyuria is evident and eventually approximates 9 L/m^2/day.

In young infants, early manifestations of NDI include vomiting, anorexia, failure to thrive, recurrent fever, and constipation.[116] Recurrent episodes of hypernatremia are common in these patients and should alert to the possibility of NDI. Mean serum sodium at presentation in a study of 30 children with NDI was 158.5 ± 9 mmol/L (range 142–176 mmol/L).[116] Early infancy is a critical period, since affected babies are dependent on others for access to fluid and have protracted sleep requirements. By a few weeks of age, affected infants may repeatedly lose 10% of their body weight overnight (Figure 21.12). Sustained dehydration and hypernatremia cause failure to thrive and there is a high risk for brain injury, developmental delay, or death during intercurrent illness.[116] Non-obstructive hydronephrosis, caused by a high urinary flow, may be the initial manifestation in some patients.

Diagnosis

Diagnosis of NDI is suspected in a patient with a clinical history of polyuria. Urine osmolarity is usually between 50 and 100 mOsm/L, even in the first morning urine. Diagnostic water deprivation is not appropriate in infants, since affected patients may become dangerously dehydrated. Unresponsiveness to intravenous infusions of DDAVP, given at a dose of 0.3 μg/kg, distinguishes NDI from hereditary forms of central diabetes insipidus due to mutations of the *AVP* gene. The DDAVP challenge test should be avoided in states of symptomatic dehydration, since these patients may be able to increase urine osmolality >300 mOsm/kg under these clinical circumstances, and erroneously suggest the diagnosis of central DI rather than NDI. Ultrasonography is important to rule out obstructive uropathy and renal dysplasia, which can also cause polyuria. Fractional sodium excretion, persistent urine osmolarity <100 mOsm/L, and normal serum renin are usually sufficient to distinguish NDI from neonatal Bartter syndrome. Gene testing for *V2R* mutations is now available commercially and is recommended.

Treatment

Early intervention with aggressive water supplementation through continuous overnight nasogastric or gastrostomy feeding may be required in young infants to prevent recurrent dehydration. Older children and adolescent patients may be able to compensate for high urinary volume by drinking adequate amounts of water. However, risk of decompensation exists during acute illnesses when demands of oral intake are not adequately met. Treatment with low-dose oral hydrochlorothiazide (1 mg/kg/day) creates a chronic mild salt deficit, stimulates renin production, enhances proximal water reabsorption and paradoxically reduces urine volume. Prostaglandin inhibitors such as indomethacin (2–3 mg/kg/day) may also help in decreasing daily urine output by 20–30%. The mechanism by which this class of drugs reduces renal free water excretion is not well understood. As in Bartter syndrome, selective COX-2 inhibitors (celecoxib and rofecoxib) are effective and cause less gastrointestinal toxicity but are not currently available for clinical use in children.

The enormous free water requirement for infants with NDI may easily interfere with caloric intake and usually requires careful nutritional assessment. In our experience, these infants suffer from a feeding disorder characterized by difficulty in the transition to solid foods. Toilet training is commonly delayed and in a small number of patients progressive bladder dysfunction may lead to severe hydronephrosis (Figure 21.13) and decline in renal function. Since intermittent self-catheterization and continent urinary diversion are not practical options, medical therapy should be aggressively optimized.

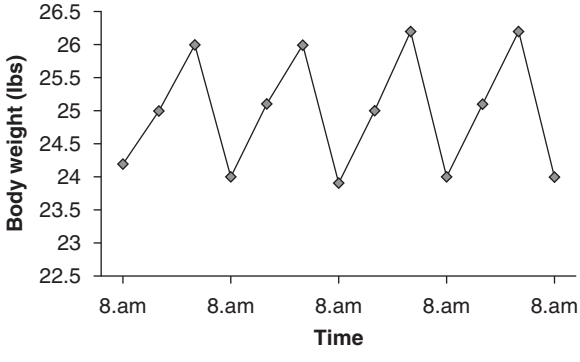

Figure 21.12 Nephrogenic diabetes insipidus is associated with complete unresponsiveness of vasopressin-dependent water reabsorption via aquaporin channels in the collecting duct. Massive polyuria (9 L/m²/day), particularly in infants, can lead to dehydration. This figure shows repeated overnight water losses approximating 10% of the body weight in this patient.

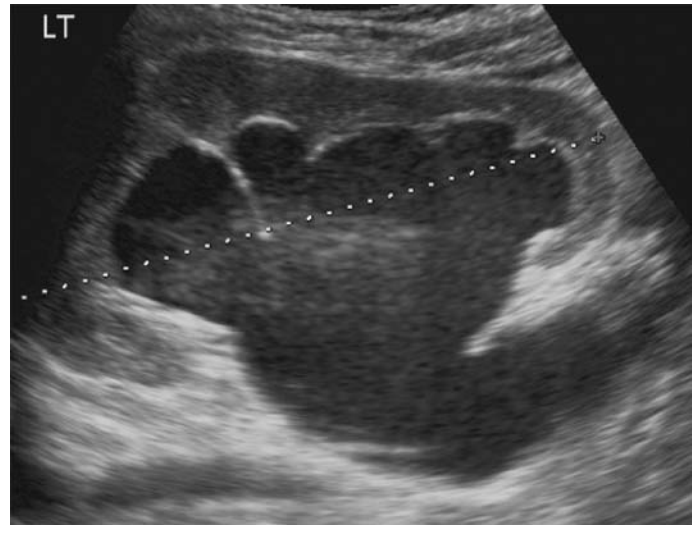

Figure 21.13 Massive polyuria in NDI can result in bladder decompensation and progressive hydronephrosis. This ultrasound demonstrates hydronephrosis with pelvicalyceal dilatation in a patient with NDI. Loss of renal function can result from prolonged bladder dysfunction and hydronephrosis and may require urologic intervention.

Concluding remarks

Precise diagnosis of renal tubular disorders may, in the future, rely increasingly on molecular genetic testing. Internet sites such as www.genetests.org list commercial and research laboratories where such tests may be sought. However, the crux of diagnosis and therapy will always depend on initial recognition of renal tubular dysfunction and careful characterization of the precise disturbance of transport physiology.

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Part V

Renal failure

22 Chronic kidney disease

Craig S Wong and Robert H Mak

Given the increasing prevalence of end-stage renal disease (ESRD) in adults, chronic kidney disease (CKD) has become a public health concern in the United States. Children (less than 20 years) account for about 2% of the entire ESRD population in the country.[1] As of 2004 the prevalence of ESRD in patients less than 20 years has grown by 22% since 1992, compared with the 56% increase in prevalence for the total ESRD population.[1] Although small in number compared with adults, pediatric patients with CKD require greater amount of resources, specialized care, and time in order to achieve optimal outcomes.[2] CKD in children is the result of heterogeneous diseases of the kidney and urinary tract that range from common congenital malformations of the urinary tract, to rare inborn errors of metabolism that effect kidney function. The challenges facing physicians treating children with CKD are compounded by the need to pay a close attention to growth, development, and social maturation.

Definition of chronic kidney disease in children

The National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) established a conceptual framework for identification, management, and the care of all patients with CKD and those who are at risk for kidney failure.[3] CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73m^2 for 3 months or more, regardless of the underlying etiology (Table 22.1). The current definition of CKD encompasses all of the patients who were classified as having chronic renal failure (CRF) and chronic renal insufficiency (CRI). Patients with a GFR of ≤ 75 ml/min/1.73 m^2 are now categorized in CKD stages 2–4.

Kidney damage is defined as structural or functional abnormalities of the kidney, initially without decreased GFR, that can lead to a future decrease in kidney function; and is identified by abnormalities in the blood, urine, imaging tests, and renal biopsy (Table 22.2). The broader implications of this common definition for CKD is that patients are identified earlier with their kidney disease, which may prolong their native kidney function and improve their long-term health. To achieve these aims, a CKD staging system has been developed, with an associated action plan for each stage (Table 22.3). It is important to note that the CKD stages only apply to children 2 years old and above.

Table 22.1 K/DOQI criteria for definition of chronic kidney disease in children[a]

A patient has CKD if either of the following criteria are present:

1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, indicated by one or more of the following:
   - Abnormalities by kidney biopsy
   - Abnormalities based on imaging tests
   - Abnormalities in the composition of the blood or urine.
2. GFR <60 ml/min/1.73m^2 for ≥3 month, with or without the signs of kidney damage listed above.

[a]Adapted and reproduced with permission from Pediatrics 111:1416, 2003.[3]

Epidemiology of chronic kidney disease

It is important to recognize that underlying causes for CKD are significantly different in children than those seen in adults. Diabetic nephropathy and hypertension, which are the dominant causes of CKD in adults, are very rare causes of CKD in childhood. As a group, the leading causes of CKD in children are congenital and urologic anomalies, especially in the youngest age groups.[4–6] The 2005 data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) chronic renal insufficiency (CRI) registry show that as age increases, the proportion of patients with congenital urologic anomalies decrease and those with glomerular diseases as an etiology increases (Figure 22.1). These data also demonstrate that CKD in childhood tends to affect more males than females, with males representing 64% of the total affected population. Racial distribution of childhood CKD in the NAPRTCS registry is as follows: 61% Caucasian, 19% African-American, and 14% Hispanic.[4]

Table 22.2 Markers of kidney damage

Blood:
- Serum creatinine elevation
- Blood urea nitrogen (BUN) elevation
- Hypoalbuminemia
- Hyperuricemia
- Hypo- or hypernatremia
- Hypo- or hyperkalemia
- Hypo- or hyperphosphatemia
- Metabolic acidosis

Urine:
- Microalbuminuria
- Proteinuria
- Hematuria
- RBC casts
- Pyuria
- WBC casts
- Tubular cells
- Granular casts
- Lipid

Imaging:
- Increased echogenicity
- Small, 'hyperechoic' kidneys
- Absence of one kidney
- Acute pyelonephritis
- Kidney scarring
- Large kidneys
- Kidney size disparities
- Hydronephrosis
- Urinary obstruction
- Renal artery stenosis
- Nephrocalcinosis
- Urinary calculus disease
- Cystic kidney diseases
- Medullary sponge kidney

Pathophysiology of chronic kidney disease

Divalent ion metabolism and bone disease

The kidney plays an important role in bone and mineral homeostasis. It regulates calcium and phosphorus balance, participates in the catabolism and regulation of parathyroid hormone (PTH), and synthesizes 1,25-dihydroxy $(OH)_2$ vitamin D_3 (1,25 $(OH)_2$ D_3). Renal osteodystrophy encompasses a spectrum of high- to low-turnover skeletal lesions. The impact of therapy may change the histologic pattern.

As CKD progresses, secondary hyperparathyroidism develops as a result of several factors: phosphate retention, hypocalcemia, impaired renal $1,25(OH)_2D_3$, alterations in PTH secretion, skeletal resistance to the calcemic actions of PTH, and alterations in the calcium-sensing receptor. Phosphorus retention increases the secretion of PTH indirectly by lowering serum ionized calcium levels and also by reducing renal synthesis of $1,25(OH)_2D_3$ through inhibition of the enzyme 1 α-hydroxylase in the proximal tubules. Normal serum phosphorus concentration is maintained in mild to moderate CKD by increasing PTH levels, thus attempting to increase urinary phosphate excretion. Hyperphosphatemia usually develops in CKD stages 4 to 5.

Adynamic, or low-turnover, bone disease was initially recognized as a side effect of aluminum-containing phosphate binders used in patients with CKD. Aluminum excretion diminishes with declining renal function and this ion accumulates in the face of CKD, leading to osteomalacia. Over the last two decades, aluminum-containing phosphate binders have not been in clinical use. Adynamic renal osteodystrophy is now recognized as a side effect of calcium-containing phosphate binders and aggressive vitamin D analogue therapy. Adynamic bone disease represents a state of relative hypoparathyroidism and presents clinically with hypophosphatemia, transient

Table 22.3 NKF-K/DOQI classification of chronic kidney disease[a]

CKD stage	GFR (ml/min/1.73m^2)	Description	Action plan[b]
Normal renal function	≥90	If risk factors for CKD are present, proceed with action plan	Screening, CKD risk reduction
1	≥90	Known kidney damage with normal or increased GFR	Diagnose and treat primary and comorbid conditions, slow CKD progression, and reduce cardiovascular risk factors
2	60–89	Kidney damage with mild reduction of GFR	Evaluate rate of decline in GFR
3	30–59	Moderate reduction of GFR	Evaluate and treat complications of CKD
4	15–29	Severe reduction of GFR	Prepare for kidney replacement therapy
5	< 15 (or dialysis)	Kidney failure	Kidney replacement therapy

[a]For billing purposes, Center for Medicare Services (CMS) recommends defining stage V as patients with severe reduction of GFR (<15 ml/min/1.73m^2) who are not yet on dialysis and stage VI as those who have begun dialysis.
[b]Includes actions from preceeding stages.

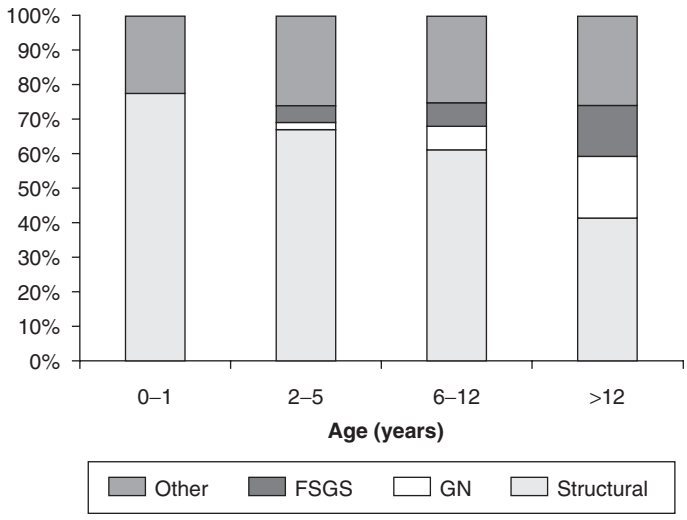

Figure 22.1 Graphic representation of etiology of chronic kidney disease by age. (Data from NAPRTCS ADR 2005.[4])

hypercalcemia, and low alkaline phosphatase. Serum PTH levels are low to normal.

Anemia

Anemia is a frequent complication of CKD in children and adults. Studies in the adult population have provided substantial evidence that anemia is an important predictor of morbidity and mortality, often in association with cardiovascular disease (CVD). Anemia is commonly present early in the course of CKD, long before the need for renal replacement therapy. Anemia has also been associated with impaired cognitive function in adults with renal insufficiency.[7] Of possibly even greater significance, higher hematocrit values in patients over 18 years of age with CKD have been correlated with a decreased risk for patient morbidity (e.g. hospitalization) and mortality.[8]

Remarkably, anemia present in children with CKD has received little attention. Recent data from the United States Renal Data System (USRDS) revealed the mean hematocrit value is generally less than 30% at the time of dialysis initiation; possibly reflecting suboptimal anemia management in CKD prior to dialysis.

Previous publications from the NAPRTCS have documented that the hematocrit of a substantial percentage of children with CKD does not meet the target value of 33–36% recommended by the NKF's K-DOQI.[9] Hematocrit of less than 33% in children with CKD has been associated with an accelerated rate of progression towards ESRD.[10] In another NAPRTCS study, Warady and Ho determined that a hematocrit less than 33% at dialysis initiation was not only associated with a greater mean number of hospitalization days within the initial year of dialysis but was also associated with a significantly greater probability for a hospitalization of 30 days or more during that year.[11] In addition, there was an estimated 52% greater risk of death in association with the presence of anemia.[11]

Nutrition

Cachexia is a common problem in patients with CKD. It is characterized by loss of lean body mass and high metabolic rate despite inadequate dietary intake. The term malnutrition, which implies that abnormalities can be reversed by provision of appropriate nutrition, inadequately describes the pathologic state of cachexia in CKD. The etiology is multifactorial. Metabolic acidosis, insulin resistance, and increased cytokine expression stimulate muscle protein loss by mechanisms that work independent of the impact of anorexia.[12]

Several studies have shown that the majority of children with CKD exhibit an inadequate dietary energy intake. Furthermore, the energy intake progressively declines with worsening renal failure. Since energy intake is the principal determinant of growth during infancy, poor nutrition is considered to be an important factor responsible for growth impairment in children with congenital disorders leading to CKD.[13–15]

Anorexia is commonly seen in patients with CKD and ESRD, and has been attributed to the presence of 'middle molecules' in patients with renal dysfunction.[16] Although the identity of these anorexigenic molecules in uremic serum is unknown, administration of a mixture of them into rodents causes reduction in carbohydrate intake.[17] Other potential causes of anorexia in CKD include an inability to distinguish flavors, gastric irritation caused by medications, hemodynamic instability as a result of antihypertensive therapies, a sensation of fullness during peritoneal dialysis, and psychologic and economic factors.[16] Elevated circulating levels of leptin, which mediate its effects through the central melanocortin system, may be an important cause of cachexia in CKD.[18]

Energy intake below 80% of recommended dietary allowance (RDA) correlates with growth failure in children with CKD.[13,19] However, augmentation of energy intake above the RDA can result in obesity, rather than an acceleration of linear growth.[20,21]

Growth

Growth failure has long been recognized as one of most common and profound clinical manifestations of CKD in infants, children, and adolescents. Multiple factors that contribute to growth retardation are age at onset of CKD, type of primary renal disease, concomitant metabolic acidosis, malnutrition from calorie deprivation, anemia, renal osteodystrophy, and perturbations of the growth hormone (GH) and insulin-like growth factor (IGF) axis.[22] The observation that recombinant human growth hormone (rhGH) treatment improves the growth velocity of children with CKD has dramatically changed the therapeutic approach to the growth retardation of CKD.[23] Since a positive change in standardized height (so-called catch up growth) is unlikely to occur in association with dialysis, despite the use of rhGH, and typically only occurs in the youngest (less than 6 years) transplant recipients, the

potential achievement of a normal adult height in patients with impaired kidney function mandates aggressive attention to growth and the use of rhGH in the predialysis phase of CKD.[24]

Growth failure in infants, children, and adolescents with CKD may be a risk factor for a poor patient outcome. Wong et al, utilizing the USRDS Pediatric Growth and Development Special Study, demonstrated that poor incremental growth was associated with an increased risk of death in children with ESRD.[25] Furth et al., utilizing the USRDS data, also demonstrated that children with growth failure had an increased risk of morbidity, with a 14–25% increased risk of hospitalization, compared to patients with normal growth.[26] Analysis of 1988 children under 21 years of age, enrolled in the dialysis arm of NAPRTCS, has shown similar results.[27] Hence, children with significant growth impairment due to ESRD (<2.5 SD below normal for age and gender) have a twofold higher risk of death compared to dialyzed children with a more normal height.[25,26] The more severely growth-retarded patients also had more hospital days per month of dialysis and were less likely to attend full-time school.[26] Consequently, growth retardation, which may be a reflection of suboptimal medical care of patients with CKD, should be regarded as a potential risk factor for increased morbidity and mortality in children with CKD.

Metabolic acidosis

The kidney is an important organ in the excretion of net acid load produced by normal metabolism. An overt metabolic acidosis is common in patients with an estimated GFR <30 ml/min/1.73 m^2. Metabolic acidosis due to CKD may stem from a number of abnormalities: reabsorption of filtered bicarbonate, reduction in ammonia synthesis, decreased excretion of titratable acid, and decreased acidification of tubular luminal fluid by the distal nephron. Type IV renal tubular acidosis, as a result of loss or insensitivity of aldosterone receptors in the renal tubules, is also common in advanced stages of CKD.

Chronic metabolic acidosis produces a change in the ionic composition of bone, with net reductions in apatite, sodium, and potassium. Chronic metabolic acidosis causes alterations in cellular bone activity, resulting in a decrease in osteoblastic bone formation, while osteoclastic bone resorption is enhanced.[28] Additionally, the trophic effects of the growth hormone IGF-I axis on bone growth and structure is blunted in chronic metabolic acidosis.[29] Chronic metabolic acidosis also reduces the proximal tubular synthesis of $1,25(OH)_2D_3$, with negative impacts on divalent ion balance, PTH, and bone metabolism.

Hormonal perturbations

Growth hormone

CKD is associated with significant abnormalities of the GH IGF axis. Although CKD is not a state of GH or IGF-I deficiency, the regulation and bioavailability of the components of the GH and IGF system are altered. Indeed, reduced metabolic clearance of GH results in a rise in circulating GH levels. Available evidence suggests that the GH resistance seen with CKD may be caused by a combination of (1) down-regulation of GH receptors (GHR) in liver and the growth-plate[22] and (2) defective GH post-receptor signaling involving impaired phosphorylation of STAT 5 (signal transducer and activator of transcription) in the skeletal muscles.[30] Furthermore, increased levels of IGF binding proteins may limit the bioavailability of IGF-I. Proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), can also cause GH resistance by down-regulating GHR and impairing GH signaling at the same step of STAT 5 phosphorylation. The precise role of these cytokines in abnormalities in GH metabolism and their impact on growth is not entirely clear at this time.

Insulin

Insulin resistance is common in children with CKD. The major site of this resistance is the peripheral tissues, mainly the skeletal muscle.[31] Circulating toxins in CKD may be responsible for the insulin resistance, which has been shown to improve after the initiation of dialysis. Correction of acidosis,[32] anemia,[33] and hyperparathyroidism,[34] as well as low protein diets,[35] may improve insulin resistance and correct glucose tolerance. Peritoneal dialysis is more effective than hemodialysis in improving insulin resistance with ESRD.[36]

Thyroid functions

Thyroid hormone concentrations, free triiodothyronine (T3), and thyroxine (T4), are low in children with CKD. Thyroid-stimulating hormone (TSH) is normal. This combination may be interpreted as a physiologic down-regulation to conserve energy. Clinically, CKD patients appear euthyroid. Supplementation of thyroid hormone is unnecessary in most patients and treatment may lead to exaggerated protein catabolism.[37]

Adrenal hormones

Dysregulation of the hypothalamic–pituitary–adrenal axis may be seen in CKD. Clinically evident adrenocortical insufficiency is uncommon, but may be occasionally seen in patients returning to dialysis after failure of their renal transplants. Demonstration of low cortisol levels and insufficient cortisol response to adrenocorticotropic hormone (ACTH) is required to confirm the diagnosis. Increased risk of acute adrenal insufficiency may be encountered during severe stress, such as surgical procedures or abrupt steroid withdrawal.

Progression of chronic kidney disease

Experimental and human renal diseases progress to terminal renal failure, often independent of the events responsible for the inciting injury. Histologically, progression of renal disease

is characterized by glomerulosclerosis and tubulointerstitial fibrosis. Reduction in nephron mass by renal disease causes progressive damage to the unaffected nephrons through the consequences of adaptive increase in glomerular pressure and flow, or hyperfiltration injury.

Glomerular capillary hypertension, originally serving to maintain ultrafiltration in the face of nephron loss, is a key mediator of glomerular hypertrophy and progressive glomerulosclerosis.[38] Capillary hypertension is also accompanied by enhanced transglomerular ultrafiltration of plasma proteins and proteinuria. Protein, which leaks through the glomeruli, injures the tubular cells and thereby causes interstitial inflammation and subsequent fibrosis.[39] In young animals, in which maturational growth is occurring, glomerular injury after renal ablation is more severe than in adult animals. Glomerular hypertrophy and subsequent glomerulosclerosis is more marked in deeper nephrons in the young rat. Increased glomerulosclerosis has been postulated to involve factors unique in the young growing kidney, which is characterized by centripetal growth and differentiation.[40]

Age at the time of loss of renal mass also affects the renal response in humans. Several follow-up studies conducted on renal transplant donors as well as adults who have undergone nephrectomy following trauma and unilateral disease suggest a relatively benign course after unilateral nephrectomy. In contrast, as many as 33% of children undergoing unilateral nephrectomy for Wilms' tumor develop microalbuminuria.[41] Furthermore, in children with unilateral renal agenesis, there is a significant risk for proteinuria (19%), hypertension (47%), and renal insufficiency (13%), and even death (6%).[42]

Hypertension and proteinuria are other well-established factors known to contribute to progression of renal disease and loss of renal function. The Modification of Diet in Renal Disease (MDRD) study randomly assigned 840 adults with CKD to either a usual or a low blood pressure goal, and then compared the rates of decline in GFR.[43] Those patients randomized to a lower blood pressure goal had significantly reduced proteinuria and had a slower decline in GFR. The results from this study support the concept that proteinuria is an independent risk factor for the progression of renal disease.[44] Other studies have also shown a similar relationship between blood pressure and progression of CKD.

Clinical manifestations

James F Goodhart, a nephrologist succeeding Richard Bright at Guy's Hospital in London, made one of the first historic descriptions of CKD in children:

> The first point I will insist upon is the frequency with which serious disease of the kidney fails in symptoms. It may be possible to overlook very chronic cases in children by reason of this very absence of symptoms.[45]

Indeed, many children with CKD do not manifest clinically until their renal failure is advanced. In many patients the diagnosis is first made during an emergency room visit for a complication of CKD, such as bone pain, anemia, or vomiting resulting from uremic gastritis.

Clinical manifestations of CKD are the consequence of metabolic derangements that accompany failure of kidney functions, and accumulation of known and unknown 'uremic toxins'. Poor linear growth and short stature are the most well-recognized clinical features of long-standing CKD. While renal osteodystrophy may remain asymptomatic in some children with CKD, bone pain, difficulty in walking, and skeletal deformities may be prominent symptoms in others. Poor tolerance of usual activity, being tired, poor attention span, and congestive cardiac failure can be the manifestations of anemia.

High urine output is a common manifestation in patients with congenital urinary abnormalities or tubulointerstitial disorders. New onset of enuresis can be an early manifestation of concentrating defect seen in CKD, and should always be investigated. Oliguria is generally present in those with underlying glomerulonephritis or nephrotic syndrome. Poor nutritional intake, resulting in calorie-protein malnutrition, is a prominent manifestation in some patients with CKD. Need for a large volume of nutrition-poor free water to compensate for high urine output can further compromise the nutritional state in some patients.

Uremic encephalopathy, gastritis, pericarditis, and neuropathy can develop in the advanced uremic state. These complications are especially common if dialysis therapy is delayed, or clearance of uremic 'toxins' in dialysis is inadequate. As noted above, some patients present for the first time with such advanced complications.

Management of chronic kidney disease

The goals in the management of CKD are to treat the primary cause of kidney impairment, eliminate or minimize associated comorbid states, prevent or abate the loss of kidney function, treat the metabolic disturbances associated with CKD, prevent and treat cardiovascular disease, and optimize normal growth and development (Table 22.4). The complexity of care, economic demands, and emotional burden to the patients and their families tend to increase as CKD advances.

Team approach

In order to optimize outcomes for children and adolescents at all stages of CKD, the care needs to be provided by a multidisciplinary team. This team should consist of a nurse who functions as the team care coordinator, renal dietician, social worker, surgeon who specializes in the area of vascular surgery and placement of PD catheters, and a pediatric nephrologist.[46] Other members of the team who may provide periodic care should include a pediatric urologist, transplant surgeon, child-life therapists, and school counselors and educators (Figure 22.2).

Table 22.4 Guidelines for evaluation and treatment of children with chronic kidney disease[a]

I. Patients with CKD should be evaluated to determine:
   a. Diagnosis (type of kidney disease)
   b. Comorbid conditions
   c. Severity, assessed by GFR
   d. Complications, related to level of GFR
   e. Risk factors for loss of kidney function
   f. Risk factors for cardiovascular disease

II. Treatment of CKD should include:
   a. Specific therapy, based on diagnosis
   b. Evaluation and management of comorbid conditions
   c. Slowing the loss of kidney function
   d. Prevention and treatment of cardiovascular disease
   e. Prevention and treatment of complications related to decreased kidney function (i.e. hypertension, anemia, acidosis, growth failure)
   f. Preparation for kidney replacement therapy
   g. Treat persistent signs and symptoms of uremia with initiation of chronic dialysis or transplantation

III. Action plan should be developed for each patient, based on the stage of CKD as defined by the K/DOQI CKD classification

IV. Review of medications should be performed at all visits for the following:
   a. Dosage adjustment, based on level of kidney function
   b. Detection of potentially adverse effects on kidney function or complications of CKD
   c. Detection of drug interactions
   d. Therapeutic drug monitoring, if necessary

V. Evaluate self-management behaviors at all stages of CKD; suggested areas of discussion include:
   a. Provide verbal and written information regarding the diagnosis and treatment
   b. Identification of responsible adult to supervise medication administration, even for the adolescent patient
   c. Assess potential barriers for medication adherence (i.e. social instability, patient and family denial, financial barriers, poor communication among care providers)
   d. Address preventive health issues (i.e. need for ongoing care with their primary care provider, immunizations, smoking prevention)

VI. Patients with CKD should be referred to a specialist for consultation and comanagement. Patients with a GFR <30 ml/min/1.73m^2 should be referred to a pediatric nephrologist

[a]Table adapted from National Kidney Foundation. Part 1. Executive Summary. Reproduced with permission from Am J Kidney Dis 39:(S1) S24–5, 1997.[111]

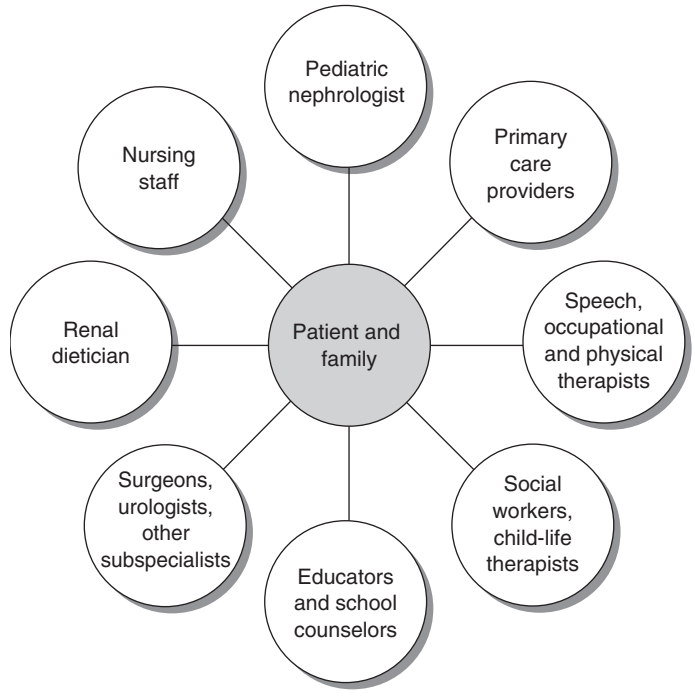

Figure 22.2 The multidisciplinary care model for children with chronic kidney disease.

Care of individuals at increased risk for CKD

Children and adolescents who are at an increased risk for CKD, but without kidney damage (e.g. single kidney, diabetes mellitus) and with normal kidney function, should undergo regular screening for appropriate markers of kidney damage (see Table 22.2) and to estimate the level of GFR. These patients are advised to follow a program of risk factor reduction, if needed, and have regular screening for CKD. Hypertension is not included as part of the CKD staging, but is known to be a sign of kidney damage as well as a risk factor for progression of renal disease and development of cardiovascular disease. Patients who are at increased risk for CKD should undergo regular screening for hypertension.[47] Children or adolescents with high blood pressure should also be carefully evaluated for CKD.

Nutrition

Evaluation and management of nutrition and growth are an essential part of the care of children and adolescents with CKD. The renal dietician assesses and develops the dietary prescription that will provide the appropriate calorie, protein, fluid, and electrolyte intake necessary for the patient's age and the degree of kidney impairment. In infants, optimizing nutrition may require placement of either a nasogastric or gastrostomy tube feeding. For patients with polyuria and renal salt wasting, a sufficiently high intake of water and provision of additional sodium (as sodium chloride or sodium bicarbonate) is recommended in order to optimize growth.[48] However, some reports have raised concerns regarding excessive sodium intake being a risk factor for decline in kidney function.[49]

Oliguric children with CKD are at risk for volume overload and hyperkalemia, and often require dietary restriction of fluid, sodium, and potassium. However, with severe dietary restrictions, palatability of food suffers and decline in caloric intake may lead

to malnutrition. In order to prevent malnutrition, early initiation of dialysis may be considered for such patients.

Growth hormone therapy

Linear growth should be evaluated at regular intervals in children with CKD. If growth continues to be suboptimal after correction of fluid, electrolyte, and acid–base balance, rhGH therapy should be considered. Treatment with rhGH is indicated in children with CKD (corrected GFR less than 75 ml/min/1.73 m^2) and presence of well-documented growth retardation (standard deviation score (SDS) <–2.0). Provocative testing for GH is not required in children meeting the above clinical criteria. The recommended dose of rhGH is 0.05 mg/kg/day, given subcutaneously for 6 days of the week. A pause of treatment is recommended in children on rhGH who have reached the 50th percentile for parental height. Resumption of rhGH is indicated if a significant reduction in growth velocity is observed after cessation of therapy. Guidelines for initiating rhGH therapy are given in Table 22.5.

Limited data are available on the efficacy and safety of rhGH therapy in infants < 2 years of age or in adolescents during puberty.[50–52] Potential complications of rhGH therapy include intracranial hypertension, aseptic necrosis, slipped femoral epiphyses, and malignancy.[53]

Growth failure often worsens while children are on dialysis. These children are also less likely to have a favorable response to rhGH while on such a therapy.[54,55] The factors responsible for poor response to rhGH in children on dialysis are not clear. Some studies have suggested that the dose of delivered dialysis might influence the efficacy of rhGH in children on dialysis.[56]

Growth retardation can persist even after renal transplantation in some children, especially those who are older children. Corticosteroid avoidance in pediatric kidney transplantation has been suggested to improve growth.[57] Treatment of short stature in the pediatric kidney transplant population has been shown to improve growth. Although concerns about precipitating acute rejection or accelerating chronic allograft nephropathy were raised in earlier studies, these concerns have been allayed in recently published studies.[58–60]

Table 22.5 Guidelines for growth hormone use in chronic kidney disease

Indications:
- Children with permanent kidney impairment (GFR <75 ml/min/1.73m^2) and
- Presence of growth retardation (SDS more negative than – 2.00)
- And/or height velocity below the 25th percentile
- No stimulation test of growth hormone is required

Recommended dosage:
- Growth hormone administered at 0.05 mg/kg/day subcutaneously 7 days per week.

Other considerations:
- Fluid and electrolyte imbalances should be corrected
- Maintain optimal nutritional intake
- Treat renal osteodystrophy and metabolic acidosis
- Obtain bone age and baseline radiographs of the hips and knees
- Observe for acute side effects, such as headache and increased intracranial hypertension

Anemia management

Anemia in CKD can be effectively corrected by use of human recombinant erythropoietin (EPO) therapy and iron supplementation. EPO can be administered either subcutaneously, intravenously, or intraperionteally. EPO is usually administered by a subcutaneous injection in patients who have CKD, or those who are on peritoneal dialysis. In hemodialysis patients, EPO is administered via intravenous route during dialysis. The frequency of administration of EPO can vary from once to three times per week. Subcutaneous use of EPO prolongs its half-life, and a decrease in total weekly dose.

EPO is usually initiated with a weekly dose of 300 units/kg, divided into three separate doses. Once the hemoglobin (or hematocrit) has reached the target range, the frequency of the EPO administration can be decreased to twice, or even once weekly. Maintenance dose of EPO varies between 60 and 600 units/kg/week.[61] Younger children and infants generally require a higher dose of EPO.[62] Ongoing blood loss, infection or inflammation, secondary hyperparathyroidism, and iron deficiency induce EPO resistance and a higher dose may become necessary for an adequate therapeutic response. An EPO preparation with a longer half-life (Aranesp) has been recently introduced, but data on safety and efficacy in children with CKD is limited.[63]

Target hemoglobin of 11–12 g/dl (hematocrit of 33–36%) is recommended by the K/DOQI.[61] In order to achieve and maintain this target hemoglobin/hematocrit, sufficient iron needs to be administered to maintain transferrin saturation (TSAT) of greater than 20% (range 20–50%), and a serum ferritin level of above 100 ng/ml (range 100–800 ng/ml). It takes 3–4 weeks for EPO to commence an improvement in hemoglobin at the initiation phase. In case of a suboptimal response to therapy by 4 weeks, the dose of EPO should be increased. During the initial 3 months of EPO therapy, the TSAT and the serum ferritin should be checked every month in patients, especially in those not receiving intravenous iron. Following attainment of the target hemoglobin/hematocrit, TSAT and serum ferritin evaluation should be determined at least every 3 months. For CKD patients not treated with EPO, and whose TSAT is greater than 20% and serum ferritin is greater than 100 ng/ml, iron status should be monitored every 3–6 months.

Treating renal osteodystrophy

In CKD patients with hyperparathyroidism, nutritional instructions for limiting dietary phosphate intake should be

the first step. If this is ineffective in improving the serum phosphorus and the hyperparathyroid state, phosphate binders to bind dietary phosphorus are recommended. Calcium-based phosphate binders have been used in the last two decades as the standard of care. However, calcium-based phosphorus binders have been associated with increased risk of vascular calcification.[64] Recently non-calcium-based phosphate binders have been shown to be equally effective in controlling hyperphosphatemia and hyperparathyroidism without causing hypercalcemia.[65] Calcitriol, or one its analogues, should be used to treat hyperparathyroidism.

The ideal target range of PTH level in predialysis CKD in children is unclear. Although there is a theoretical risk of adynamic bone disease with PTH concentrations in the normal range, normal PTH concentrations have been associated with normal growth in children with predialysis CKD.[66] Renal osteodystrophy is further discussed in Chapter 23.

Correcting metabolic acidosis

Serum levels of bicarbonate should be monitored in patients with advanced CKD (stages 3, 4, and 5) and patients on maintenance dialysis. Serum bicarbonate levels should be maintained above 22 mmol/L in order to prevent bone disease and to ameliorate excess protein catabolism.[67] Use of exogenous alkali salts containing citrate may increase the absorption of dietary aluminum in patients with CKD, in addition to increasing the net sodium burden in the patient.

Evaluating non-compliance

As succinctly summarized in a review on non-compliance by Nevins:

> Human nature dictates patients will continue to accidentally or even intentionally miss medication doses … medication noncompliance is likely to remain a ubiquitous challenge.[68]

Once patients with CKD are committed to an established treatment regimen, evaluating the patient for adherence to the prescribed medication is an essential part of ongoing care. Patients with CKD are at high risk for non-compliance due to a number of factors, including the asymptomatic nature of CKD, chronicity of illness, increasing restrictions on dietary intake, need to take multiple medications, and complexity of care associated with advancing stages of CKD. The risk factors associated with poor compliance and non-compliance are given in Table 22.6.

Traditional interventions for non-compliance involve the patient and his/her family. Lack of adult and parental supervision, which is an important factor for non-compliance in children, should be addressed.[69,70] Behavior problems in the child with CKD, parental neglect of treatment, elevated parental stress level, and dysfunctional parent–child interactions also need to be addressed in appropriate circumstances.[69,71] If non-compliance is identified, the treating team should focus on the positive, and shift from blaming the patient in order to facilitate communication and understanding. This approach is necessary in order to modify behavior and overcome barriers to therapy.[68,72]

Table 22.6 Risk factors determing patient non-compliance

Environmental factors:
- Treatment setting
- Duration of waiting time
- Continuity of care
- Congruent information
- Availability of time for information
- Availability of resources

Interrelationship factors:
- Open communication with healthcare providers
- Amount and comprehensiveness of the information
- Mutual trust and satisfaction
- Non-judgmental interviewing style

Disease and treatment factors:
- Duration of disease
- Intensity of symptoms
- Complexity of treatment
- Number of medications
- Number of doses per day
- Medication side effects
- Expense of medications
- Intrusiveness of prescribed regimen
- Lifestyle changes

Patient and family factors:
- Age, gender
- Degree of adult supervision
- Comorbid psychiatric illness
- Extent of family/peer support
- Neurocognitive abilities
- Self-esteem
- Health beliefs
- Comprehension of the treatment requirements
- Satisfaction with care program
- Prior history of non-adherence

Preventing additional kidney injury

Therapeutic interventions at earlier stages of CKD in order to prevent additional nephron loss and a decline in kidney functions have been shown to be effective in the adult population.[73–75] These strategies include blockade of the renin–angiotensin system (RAS), blood pressure control, abatement of proteinuria, strict control of diabetes, and dietary protein restriction. Many of these strategies to slow progression in

adults have been adopted in the care of pediatric patients with CKD, but only with limited data to support their use.

ACE inhibitor therapy

In experimental models of nephron loss, angiotensin-converting enzyme inhibitors (ACEIs) have been shown to protect the residual functioning nephrons from ongoing injury.[76,77] Long-term clinical studies in patients with diabetic nephropathy have documented the role of ACEIs in retarding the rate of decline of renal function.[78] This renoprotective role of ACEIs has also been noted in other clinical diseases associated with nephron loss.[73] Blockade of the RAS reduces proteinuria and interferes with the mechanisms responsible for renal fibrosis, in addition to and independent of their blood pressure lowering effects.[79,80] Angiotensin receptor antagonists (ARAs) have also been shown to provide renoprotection, similar to ACEIs.[81–83] Because of the potential for hyperkalemia, ACEIs as renoprotective therapy should be avoided in advanced CKD with GFR less than 30 ml/min/1.73 m^2.

Preventing infection

For children with congenital uropathies, the prevention of urinary tract infections (UTIs) should be included as a part of ongoing care. These strategies include antimicrobial prophylaxis for UTI, treatment of dysfunctional voiding, and referral to pediatric urology for surgical interventions, when necessary.

Avoiding nephrotoxic injury

Avoidance of nephrotoxic agents, both prescribed and over-the-counter preparations, is strongly advocated for patients with CKD. Because of their adverse impact on residual renal function, potential for acute renal failure, and possible interactions with ACEIs, patients with CKD should be counseled to avoid non-steroidal anti-inflammatory drugs (NSAIDs).[84–88]

Repeated episodes of dehydration can adversely impact renal function in patients with high-output CKD. Parents of such patients should be counseled about the importance of maintaining good hydration in preserving residual renal function.

Patients with CKD undergoing radiographic procedures that require the use of intravenous ionic contrast are at a higher risk of nephrotoxic acute renal failure and further loss of renal function.[89] Current recommendations in such patients are to provide adequate hydration before and after the contrast-associated procedure.[90] The additional renoprotective benefit of therapies such as *N*-acetylcysteine or sodium bicarbonate has been suggested but remains unclear at the present time.[91–93]

Families of children with CKD should be educated regarding the possibility of drug interactions between prescribed medications and alternative drug therapies. Many alternative therapies have been shown to be nephrotoxic, and parents need to be cautioned about their possible adverse impacts on kidneys. Unfortunately, most alternative therapies do not list their side effects, or their nephrotoxic nature, on the packaging. A side-effect profile of these alternative drugs, especially herbal agents, can be found in most poison control databases.

Managing hypertension

Hypertension is well known to adversely affect the outcome of renal disease and promote decline in renal function in both adults and children.[5,94–96] Blood pressure control is considered to be one of the core interventions for prevention of decline in renal function. As noted above, ACEIs and ARAs are ideally suited for treatment of hypertension as well as providing renoprotection. However, other additional antihypertensive agents may be necessary for adequate control of hypertension in children with renal diseases.

Protein restriction

Dietary restriction of protein has been shown to slow the decline in kidney function in adults with CKD.[74] However, available data do not demonstrate a significant benefit of dietary protein restriction in children.[95] A European multicenter trial of low-protein diet on the progression of chronic renal failure in children recruited 191 patients aged 2–18 years old and randomized them to either protein restriction (0.8–1.1 g/ kg/day), or no dietary protein restriction. At the end of 2 and 3 years of follow-up, there were no significant differences in the rates of kidney function decline between the groups.[95] Furthermore, dietary restriction of protein may interfere with growth in patients who are already at risk for poor growth.[13] At present, age-appropriate intake of protein at the RDA is recommended for children with CKD.[97]

Targeting cardiovascular risk factors

Cardiovascular diseases in adults with CKD are well known to contribute to morbidity and mortality of these patients.[98] Similar studies in children have recently demonstrated an increased risk for cardiovascular mortality in children with ESRD.[99,100] Furthermore, young adults with CKD, many of whom had onset of CKD in childhood, have also been noted to have a significantly higher risk of cardiovascular morbidity and mortality.[101–103]

Consensus guidelines for cardiovascular screening in children with CKD have not yet been developed. Adequate control of hypertension, maintaining a normal profile of blood cholesterol, and treatment of any cardiac dysfunction should be considered in all children with CKD. Table 22.7 lists the guidelines for prevention of cardiovascular morbidity in children with CKD. Hyperhomocysteinemia is a known risk factor for cardiovascular morbidity, and is commonly observed in advanced CKD and ESRD.[104] Treatment of homocysteinemia by supplemental folic acid (1–5 mg/day) should be considered in such patients.[105]

Table 22.7 Recommendations for evaluation, and management of cardiovascular risk factors in pediatric chronic kidney disease[a]

CVD risk factor	Assessment	Treatment indication	Treatment goal	Comments
Blood pressure	BP measurement	>95th percentile for age, height, and gender	<90th percentile for age, height, and gender	• Might require multiple medications • For patients on dialysis achieve dry weight • Echocardiogram yearly
Cholesterol	Fasting lipid profile yearly in children >3 years old	LDL-cholesterol ≥130 mg/dl	LDL-cholesterol <130 mg/dl	• Diet modification • If unsuccessful, medical therapy (i.e. statin) for LDL ≥160 mg/dl in postpubertal children
Tobacco use	Inquire regarding use in children >10 years old	Tobacco use	Smoking cessation	• Smoking prevention prior to use • If tobacco use, a cessation program may be helpful
Obesity	BMI at clinic visits	BMI ≥95th percentile for age and gender	BMI <85th percentile for age and gender	• Dietetic counseling • Exercise • Weight loss program
Family history	Early myocardial infarction/stroke less than age 50 years old			• Monitor risk factors closely

CVD, cardiovascular disease; LDL, low-density lipoprotein; BMI, body mass index; BP, blood pressure.
[a]Table adapted and reproduced with permission from Pediatr Nephrol 20:125, 2005.[112]

Planning for dialysis

Planning for renal replacement therapy should begin with progression of CKD to stage 4 (GFR is <30 ml/ min/1.73 m^2). At this time, the patient and the caregivers should meet with the team that will provide ESRD care and transplantation. Frequent multidisciplinary assessments must be made to determine the appropriate timing to initiate dialysis based on the child's physical and metabolic status. Assessments are also made of the caregivers' abilities and the home environment. Family support services and intervention from child psychiatrist/therapist may also become necessary in order to enhance coping mechanisms within the family unit and the patient.

Based on clinical outcome data in adults, it is generally recommended that renal replacement therapy should begin with decline of GFR to < 15 ml/min/1.73 m^2. Presence and severity of comorbid uremic symptoms, malnutrition, growth impairment, and neurocognitive dysfunction may warrant and justify earlier start of dialysis therapy.[46,106] Renal replacement therapy modality selection of either peritoneal dialysis or hemodialysis must be tailored to the needs of each child. Federal guidelines mandate discussion of renal transplantation during such modality selection meetings.

Pre-emptive transplantation

Some children may bypass dialysis and receive a pre-emptive kidney transplant. Children are more likely to be pre-emptively transplanted, as compared to adults.[107] Patients who undergo pre-emptive transplantation tend to have better graft survival than those who undergo dialysis prior to kidney transplantation.[108] Effects of race, and economic factors, and educational background have been cited as factors in a better outcome associated with pre-emptive renal transplantation.[107] Additionally, conditions that preclude patients from undergoing pre-emptive transplant (Table 22.8) tend to be associated with poorer allograft survival, once they are transplanted. Nevertheless, pre-emptive transplantation should be considered in children with available live related donors.

Rehabilitation and quality of life

Once CKD is severe enough to impair normal activities of daily living, rehabilitation of the patient with childhood-onset CKD is aimed towards integration of clinical disease management, and normal social adaptation and development. Child

Table 22.8 Relative contraindications for pre-emptive kidney transplantation

1. Conditions requiring native nephrectomies prior to transplant:
   - Uncontrolled hypertension
   - Chronically infected urinary tract with stasis
   - Persistent nephrotic syndrome
2. Patient non-compliance with medications, follow-up visits, and general ability to follow instructions
3. Catastrophic presentation with ESRD
4. Inadequate time to assess patient and family for pre-emptive transplant
5. Problems with the potential live donor:
   - Health problem identified in the donor
   - Live donor pregnancy
   - The potential recipient is allosensitized to the donor

therapists, counselors, and child psychiatrists are needed to help the child and the family unit adapt to a life of chronic illness. In addition to addressing the medical and emotional needs of these children, it is equally important to consider the educational needs of these patients. If a child's illness precludes them from maintaining full-time school attendance, hospital-based or home-based education with an adequate individualized educational program (IEP) should be considered. Maintaining a child's educational progress and participation in school is an important process for rehabilitation, as well as an important outcome measure. The ultimate goal is aimed at helping these children become independent productive adults.

Once children with CKD reach adulthood, little is known about their quality of life and their vocational rehabilitation. Among survivors of childhood ESRD, vocational placement tends to be lower compared with the general population.[109,110] Compared with their peers in the general population, the survivors of childhood ESRD have lower employment rates and are less likely to live independently of their parents.[109,110]

Satisfaction with health-related quality of life might depend on the prevalent modality of ESRD treatment. In the Dutch cohort study of kidney transplant patients with an average of 15.5 years of follow-up, the majority of patients had a very good subjective health perception.[110] In contrast, the German study of long-term follow-up consisting of 33% undergoing dialysis and 67% with kidney transplants demonstrated that these patients had a lower quality of life concerning health-related issues.[109] These studies underscore the need for concurrent psychosocial rehabilitation for our pediatric patients while they undergo medical treatment for their CKD.

Concluding remarks

Providing care to children at all stages of chronic kidney disease is complex, challenging and rewarding at the same time. Children and adolescents with CKD require greater clinical time and supervision than do adults with CKD, due to the higher disease acuity and changing maturational and developmental status. This overview of the epidemiology, pathophysiology, and general management of children with CKD provides a foundation for a further in-depth exploration of each topic, which can be found elsewhere. The care of children with earlier stages of chronic kidney disease is likely to be refined further by the advances in the molecular biology of glomerular and tubulointerstitial diseases, the use of newer immunomodulatory agents, and the data provided by current longitudinal epidemiologic studies that are under way. The latter research efforts will further improve outcomes and survival into adulthood for children with CKD.

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23 Renal osteodystrophy

Katherine Wesseling, Joel D Hernandez, and Isidro B Salusky

Since total skeletal calcium increases from about 25 grams at birth to between 900 and 1200 grams in adulthood, childhood and adolescence are a crucial time for developing a healthy skeletal system.[1] Bones are constantly sculpted and modified by two processes: modeling and remodeling. Throughout childhood, bones grow in length, wide metaphyseal regions are remodeled into narrower diaphyses, and long bones tend to drift in a lateral direction as the medial edges of bone are resorbed to a greater degree than the lateral edges. Proper bone growth requires an elaborate coordination between a number of physiologic processes, including cartilage growth, bone remodeling, and epiphyseal closure, all of which are regulated by a number of hormones, including growth hormone (GH), thyroid hormone, estrogen, testosterone, parathyroid hormone (PTH), and insulin-like growth factor (IGF).[2]

All children with chronic kidney disease (CKD), which is staged according to the National Kidney Foundation criteria based on glomerular filtration rate (GFR) (see Figure 23.1), have disordered bone modeling because the kidneys maintain the external balance of calcium, phosphorus, and magnesium, synthesize 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2 D_3$) and serve as a target organ for the action and degradation of PTH and the clearance of PTH from the circulation.[3] The term 'renal osteodystrophy' refers to the skeletal lesions that appear as renal function declines.

Clinical varients of renal osteodystrophy

Bone disease occurs early in the course of CKD, and growth failure may be the presenting symptom leading to the diagnosis of renal disease. The primary lesion of untreated renal osteodystrophy is a high-turnover lesion (osteitis fibrosa cystica) arising from excess PTH secretion. This lesion has its onset in early stages of renal insufficiency and is universally present in dialyzed children who have not begun treatment with phosphorus-binding agents and vitamin D sterols. Bone pain, deformities, growth retardation, and bone demineralization accompany osteitis fibrosa and progress as renal failure progresses, the majority of children displaying severe growth retardation (height<–2 SD of the mean for age) by initiation of dialysis.[4]

A state of low-turnover bone disease (adynamic renal osteodystrophy) also occurs in children on dialysis, although it has not been demonstrated in children with CKD. Oversuppression of bone turnover due to excess treatment with vitamin D and calcium salts is associated with normal or reduced serum PTH levels, low alkaline phosphatase levels, and high serum calcium levels.[5] Adynamic bone disease results in growth failure[6] in addition to vascular calcifications associated with early cardiac mortality.[7,8]

Pathogenesis of renal osteodystrophy

The kidneys regulate intestinal calcium absorption by converting 25-hydroxyvitamin D_3 ($25(OH)D_3$), the storage form of vitamin D, to 1,25-dihydroxy vitamin D_3 ($1,25(OH)_2 D_3$), the active form of vitamin D, by means of the enzyme 1α-hydroxylase. $1,25(OH)_2 D_3$ levels drop as renal function declines, causing hypocalcemia due to impaired intestinal and renal calcium absorption. Impaired $1,25(OH)_2D_3$ production occurs early in renal failure, decreased levels being present in children with even modest degrees of renal impairment (GFR of 50 ml/min/ 1.73 m^2).[9]

PTH secretion, regulated by serum calcium level, rises in response to hypocalcemia.[10–15] In early stages of CKD, elevated circulating PTH enhances phosphate excretion and may result in decreased serum phosphorus levels. In advanced stages of CKD, however, phosphorus excretion becomes impaired and hyperphosphatemia suppresses 1α-hydroxylase activity, further decreasing $1,25(OH)_2D_3$ production[16] and directly stimulating PTH release.[17,18] The kidneys and skeleton become increasingly resistant to the actions of PTH as renal function declines, necessitating higher levels of PTH to maintain normal mineral metabolism.[19] Prolonged stimulation of the parathyroid glands by chronic hypocalcemia and hyperphosphatemia results in parathyroid gland hyperplasia,[20] which, once established, is difficult to reverse due to the long half-life (30 years) of parathyroid cells.[21] Chronic stimulation of parathyroid glands may also lead to chromosomal changes that result in autonomous, unregulated growth and hormone release. Even in the absence of mutations, PTH secretion from enlarged parathyroid glands may

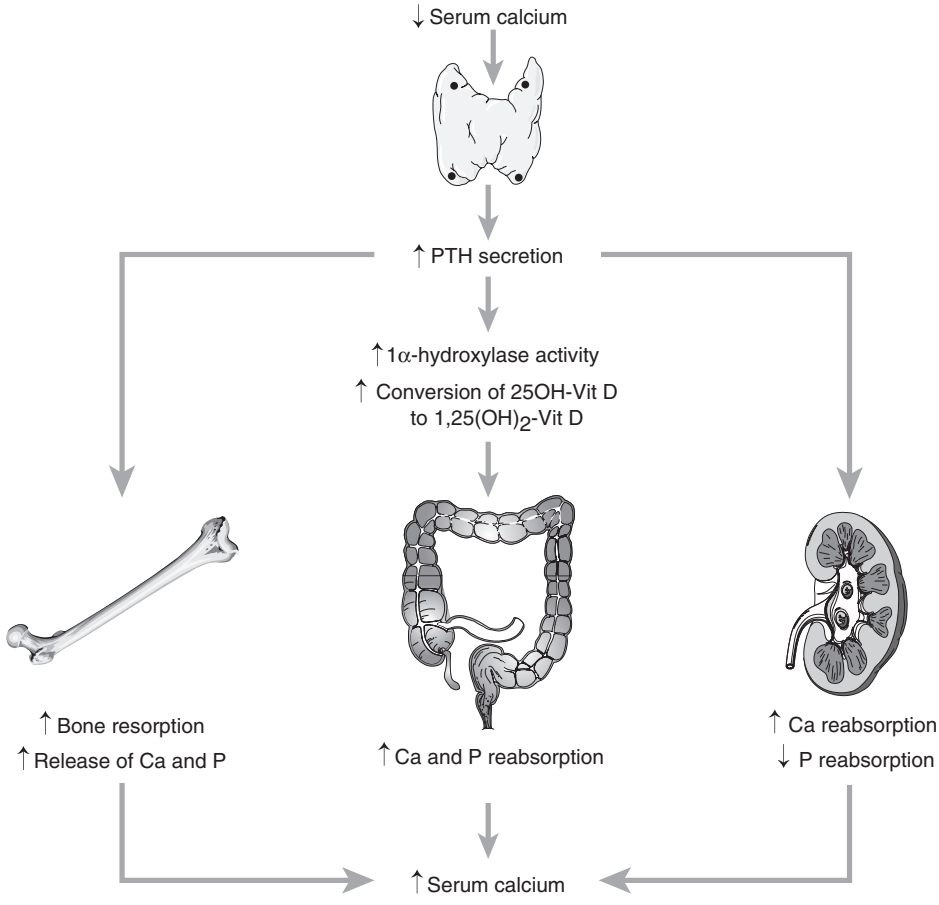

Figure 23.1 Diagrammatic representation of the pathogenesis of renal osteodystrophy.

become uncontrollable due to a non-suppressible component of PTH release from a large number of parathyroid cells. Excessively high level of PTH, acting on the skeleton, causes an increase in osteoblastic and osteoclastic activity, high rates of bone turnover, and fibrotic lesions. In summary, alterations in serum calcium, phosphorus, and $1,25(OH)_2D_3$ metabolism in CKD all contribute to dysregulation of PTH secretion, resulting in excess PTH release and bone lesions of osteitis fibrosa (Figure 23.1).

At the other end of the spectrum of renal osteodystrophy, adynamic renal osteodystrophy is a complication of treatment. Although adynamic bone has not been shown to occur in children with CKD prior to dialysis, it is a significant problem in dialyzed children treated with high doses of vitamin D and calcium salts.[6] In addition to growth failure, vascular calcifications and premature heart disease have been linked to adynamic bone.[7,22–24]

Histologic characteristics of renal osteodystrophy

Evaluation of skeletal histology provides both a method for understanding the pathophysiology of renal bone disease and a guide to its proper management. Bone tissue is obtained from the iliac crest on an outpatient basis with minimal morbidity.[25–27]

Osteitis fibrosa cystica is the histologic lesion arising from an excess of PTH.[28] The bone exhibits an increased number of osteoblasts and osteoclasts as well as peritrabecular fibrosis. An increased resorption of mineral and matrix along both the trabecular surface and within the Haversian canals of cortical bone is evident due to excess osteoclastic activity.[29]

Adynamic bone, on the other hand, is characterized by normal osteoid volume, absence of fibrosis, and a reduced bone formation rate, as evidenced by a reduced or absent double tetracycline label.[30] There is a paucity of osteoblasts and osteoclasts.[28] Adynamic renal osteodystrophy cannot be distinguished histologically from corticosteroid-induced osteoporosis, which may be present in many children due to treatment of their underlying disease. Osteoporosis, unlike adynamic bone, is associated with a decreased amount of trabecular bone and the two lesions may be differentiated on this basis.

Clinical manifestations

The symptoms and signs of renal osteodystrophy are usually non-specific, and laboratory and radiographic abnormalities generally predate clinical manifestations. Some specific symptoms and syndromes do occur, however.

Bone pain

Bone pain is a common manifestation of severe renal osteodystrophy. It often appears gradually and is aggravated by weight bearing or a change in posture. The pain associated with renal bone disease occurs most commonly in the lower part of the back, hips, and legs, but may also present with sudden pain around the knee, ankle, or heel, similar to the pain of acute arthritis. This pain is not usually relieved by massage or local heat.[3] Knee pain may be referred from hip pathology; children with knee pain should be evaluated for the possibility of slipped capital femoral epiphysis. Infants may manifest difficulty in standing, sitting, or walking.

Skeletal deformities

Bone deformities are common in uremic children because their bones undergo growth, modeling, and remodeling. Widening of epiphyses, especially around wrists, ankles, and the costochondral junctions (rachitic rosary), is commonly seen in infants (Figure 23.2). Slipped epiphyses (Figures 23.3 and 23.4), genu valgum (Figure 23.5), femoral and wrist deformities (Figure 23.6), and growth retardation are most common in preadolescent children with long-standing CKD.[4,31] Pathologic fractures of the extremities and chest wall due to osteoporosis and bony deformities may occur from minimal trauma or normal childhood activities. In addition, vertebral crush fractures convey significant morbidity in this population.

Growth retardation due to protein and calorie malnutrition, metabolic acidosis, end-organ growth hormone resistance, and renal osteodystrophy are present in many children with CKD.[32] The average height of children with even mild to moderate CKD (GFR ≤ 75 ml/min/1.73 m^2) is < −1.5 standard deviation score (SDS) of average for healthy children. Even more severe growth retardation affects younger children, with more than 50% below 5 years of age having a height SDS ≤ −1.88 (below the third percentile).[33] Growth progressively worsens as kidney function deteriorates, and, at the time of transplantation, the mean height SDS is −2.16.[34]

Extraskeletal calcifications

An association between extraskeletal calcifications and CKD has been recognized for many years, but the problem has become of increasing concern since the introduction of long-term dialysis treatment.[35] Complications of extraskeletal calcifications occur mainly in the dialysis population and predispose these children to premature heart disease.[7,8] Hyperphosphatemia, hypercalcemia, vitamin D sterol therapy, a high intake of calcium-containing salts, adynamic bone disease, and an increase in the serum calcium–phosphorus ion product have been linked to extraskeletal calcifications. As a result, careful attention should be directed at preventing oversuppression of PTH levels in children on dialysis, and serum calcium and phosphorus levels should be maintained in the normal range for age in order to

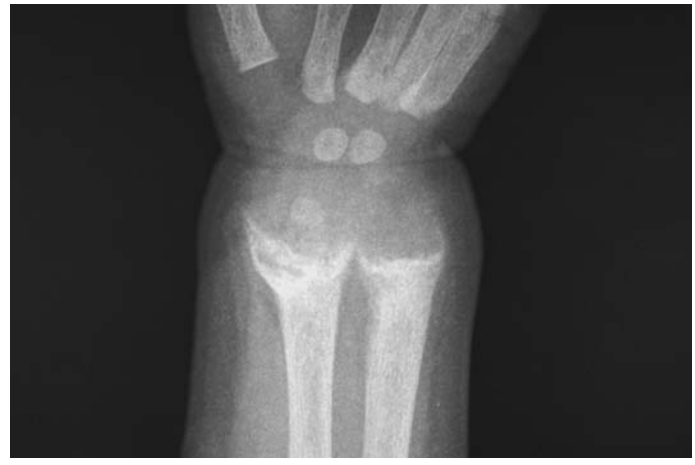

Figure 23.2 Radiograph of a patient with 'renal rickets'. The epiphyses demonstrate the characteristic widening, cupping, and fraying.

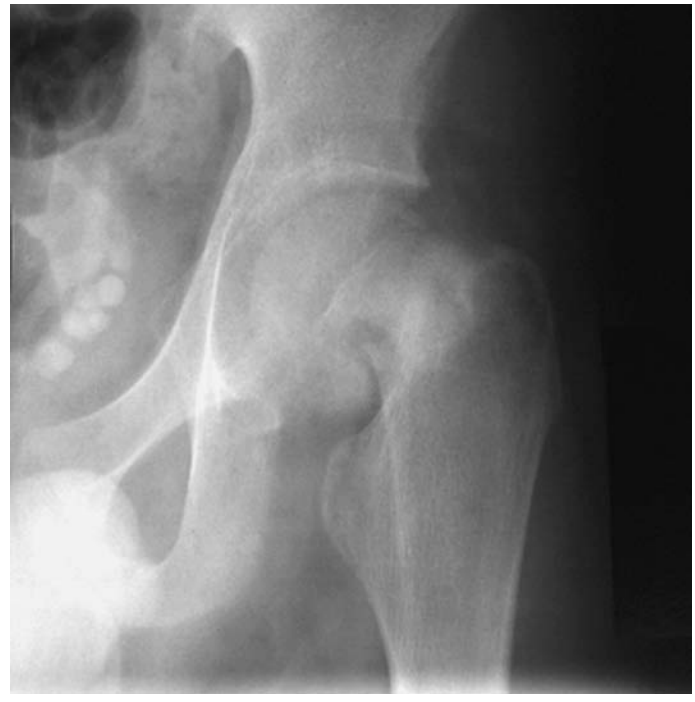

Figure 23.3 X-ray of the left hip showing slipped capital femoral epiphysis and osteopenia in a patient with renal osteodystrophy and secondary hyperparathyroidism.

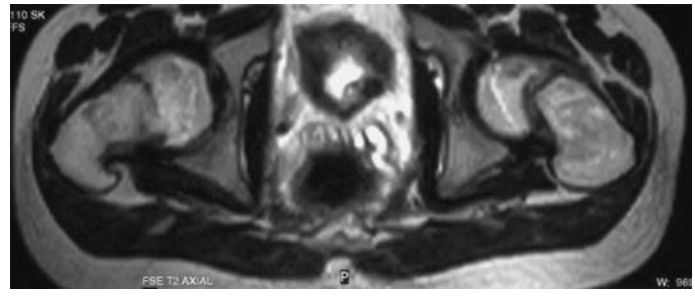

Figure 23.4 MRI of the pelvis showing slipped capital femoral epiphysis.

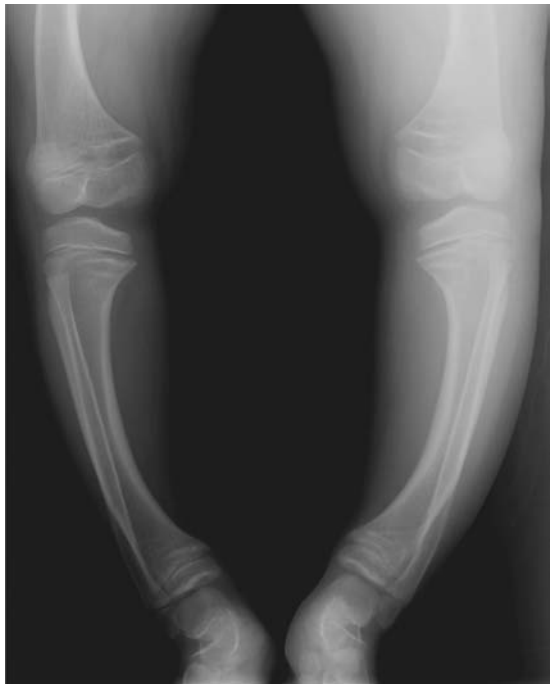

Figure 23.5 X-ray of both legs demonstrating genu valgum deformity and osteopenia in a patient with severe secondary hyperparathyroidism due to chronic renal failure.

avoid their deposition in blood vessels. Extent of vascular calcifications in children may be recorded by ultrasound evaluation of carotid intimal-medial wall thickness.[36] The methodology for coronary electron beam tomography (EBCT), which is useful in the adult population, has not been well developed for children.

Biochemical characteristics of renal osteodystrophy

Serum calcium, phosphorus, and magnesium

Hypocalcemia often occurs with the progression of renal disease due to the fall in $1,25(OH)_2D_3$ level, but resolves after initiation of calcium-containing salts and vitamin D therapy. Hypercalcemia may occur due to aggressive treatment of hyperparathyroidism with high doses of vitamin D therapy and calcium-based phosphate binders, and may also occur due to the development of adynamic bone disease.[5]

Patients with early stages of CKD may have normal or even low serum phosphorus levels due to an increase in renal phosphate excretion in response to elevated PTH level.[37–39] In advanced stages of CKD (GFR < 30 ml/min/1.73 m^2), however, renal phosphorus excretion is impaired and hyperphosphatemia ensues. As a result, patients undergoing treatment with dialysis require dietary phosphate restriction and use of phosphate-binding agents. However, due to increased rates of growth, infants and young children must maintain higher age appropriate level of serum phosphorus than older children.

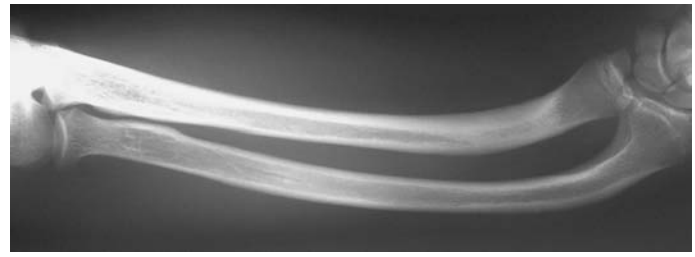

Figure 23.6 X-ray of radius and ulna in a patient with long-standing chronic renal failure and secondary hyperparathyroidism, showing deformity of the forearm as a result of renal osteodystrophy.

Intestinal absorption of magnesium is normal or slightly reduced in patients with CKD,[40] but serum magnesium levels often increase with advanced disease due to decreased renal excretion. The use of magnesium-containing laxatives should be avoided in children with advanced renal disease in order to avoid hypermagnesemia, which, if severe, may lead to apnea, refractory bradycardia, and hypotension.[41] Rarely, hypomagnesemia may develop in children with CKD and severe malabsorption or diarrhea.[40]

Plasma alkaline phosphatase activity

Serum alkaline phosphatase is a valuable marker of the severity of secondary hyperparathyroidism in children with CKD. Osteoblasts normally express large amounts of the bone isoenzyme of alkaline phosphatase, and elevated serum levels correlate with increased osteoblastic activity, increased bone formation, and high level of serum PTH.[42] Level of alkaline phosphate also increase during therapy with recombinant human growth hormone (rhGH). Since alkaline phosphatase is also present in the liver, elevated serum level of total alkaline phosphatase may not always indicate increased bone turnover. Measurement of the heat-stabile and heat-labile fractions may help to separate skeletal from hepatic causes of elevated levels. Alkaline phosphatase measurements are useful in monitoring the skeletal response to treatment with vitamin D sterols in patients with osteitis fibrosa; values that decrease over several months usually indicate histologic improvement (Table 23.1).[42]

Parathyroid hormone

Serum PTH level, measured by first-generation immunoradiometric assays (1st PTH-IMAs), is widely used as non-invasive marker in distinguishing low-turnover lesions from osteitis fibrosa.[43–45] PTH level increase as GFR declines, not only due to hypocalcemia but also due to an increasing skeletal resistance to the actions of PTH.[46–48] Down-regulation of the PTH receptor, down-regulation of osteoblast differentiation factor, and increased level of osteoclastogenesis inhibitory factor occur with decreased renal function, contributing to the skeletal resistance to PTH.[49–51]

Table 23.1 Age-appropriate normal values of serum calcium, phosphorus, and alkaline phosphatase

Age (years)	Serum phosphorous	Serum calcium (total) (mg/dl)	Serum calcium (ionized)(mM/L)	Alkaline phosphatase (IU/L)
1st year	4.8–7.4	8.8–11.3	1.22–1.4	
1–5	4.5–6.5	9.4–10.8	1.22–1.32	100–350
6–12	3.6–5.8	9.4–10.3	1.15–1.32	60–450
13–20	2.3–4.5	8.8–10.2	1.12–1.30	40–180

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Table 23.2 Target ranges of plasma PTH by stage of CKD in children

CKD stage	GFR range (ml/min/1.73 m^2)	Target intact PTH (pg/ml)
3	30–59	35–70
4	15–29	70–110
5	< 15 or dialysis	200–300

CKD, chronic kidney disease; GFR, glomerular filtration rate; PTH, parathyroid hormone.

In patients with mild to moderate CKD, PTH levels determined by 1st PTH-IMA that are within normal range generally correspond to normal rates of bone formation, whereas mildly increased levels should suggest the presence of secondary hyperparathyroidism.[52] Some evidence indicates that catch-up growth occurs when PTH levels are suppressed to within the normal range in children with stages 3 and 4 CKD.[53] However, others have found that linear growth correlates with PTH levels in this population; patients with the highest PTH values maintaining the highest rates of growth.[54] In patients undergoing maintenance dialysis who are either untreated or are receiving small daily oral doses of calcitriol, 1st PTH-IMA level of approximately three times the upper limit of normal generally correspond to normal bone formation rates.[43,44,52,55] Oversuppression of PTH in this population has also been shown to result in growth failure, hypercalcemia, and adynamic bone.[6]

In summary, it is important to maintain serum PTH level in a range appropriate for the stage of CKD (Table 23.2). Levels of PTH appropriate for early stages of CKD would be indicative of low-turnover disease in dialysis patients, and appropriate levels for stage 4 CKD represent osteitis fibrosa in mild CKD.

Radiographic features

The most consistent radiographic feature of secondary hyperparathyroidism is the presence of subperiosteal erosions.[42,56,57] The degree of subperiosteal erosion may correlate with serum PTH and alkaline phosphatase levels, but radiographs may also be normal in patients with moderate to severe histologic features of osteitis fibrosa cystica on bone biopsy.[58]

In prepubertal children with secondary hyperparathyroidism, metaphyseal changes – i.e. growth zone lesions that are termed 'rickets-like lesions' (see Figure 23.2) – are common.[56] Typical rachitic lesions, with widening of the epiphyseal growth plate and other deformities, occur in children with open epiphyses.[56] Slipped epiphyses are common and are best seen on hand and hip films (see Figures 23.3 and 23.4).[31] Avascular necrosis of the femoral head and subperiosteal erosions in the distal ends of clavicles, on the surface of the ischium and pubis, at the sacroiliac joints, and at the junction of the metaphyses and diaphyses of long bones, may also occur.[57,58] Cystic lesions may be seen on plane films, signifying long-standing osteitis with areas of bone replaced by fibrosis or 'brown tumors' (Figure 23.7), and varum and valgum deformities of the extremities are common in prepubertal children. Radiographic abnormalities of the skull in secondary hyperparathyroidism may include: a diffuse 'ground-glass' appearance, a generalized mottled or granular appearance (a so-called 'salt and pepper skull'), focal radiolucencies, and focal sclerosis.

Treatment of renal osteodystrophy

Treatment of renal osteodystrophy in children is aimed at achieving optimal growth while maintaining normal serum levels of calcium and phosphorus, preventing parathyroid gland hyperplasia, maintaining normal indices of bone remodeling, and avoiding extraskeletal calcifications. Children with secondary hyperparathyroidism and mild to moderate CKD should be treated early with correction of hypocalcemia. Vitamin D therapy should be initiated when serum intact PTH levels are elevated for stage of CKD. Dietary modifications become important in late stages of CKD and in dialyzed children to ensure adequate calcium but restricted phosphorus intake.

Phosphorus manipulation

Serum phosphorus levels decrease due to elevated serum PTH levels early in the course of CKD, whereas, in more advanced stages (stages 4 and 5), decreased glomerular filtration results

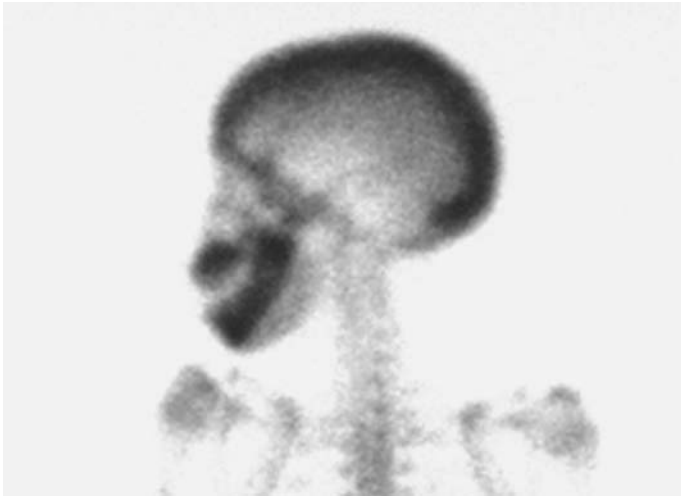

Figure 23.7 Bone scan demonstrating radioisotope uptake in the jaw and calvarium in a patient with long-standing renal osteodystrophy and hyperparathyroidism. The patient presented with a mass in the mandible, which was shown to be a 'brown tumor' by biopsy.

in hyperphosphatemia. Serum phosphorus levels, in all children, should be maintained within age-appropriate ranges (see Table 23.1), since both hypophosphatemia and hyperphosphatemia have adverse consequences. Infants, in particular, must be closely monitored for hypophosphatemia since normal levels of serum phosphorus are higher in infancy than later in childhood and intake in infancy may be limited due to ingestion of low-phosphorus formulas.[59] Bone disease, such as osteomalacia and rickets, proximal myopathy, rhabdomyolysis, and congestive heart failure have all been attributed to severe, persistent hypophosphatemia.[59,60]

As GFR declines, phosphate excretion falls. In children with CKD stages 4 and 5, dietary restriction of phosphorus becomes essential. Unfortunately, adherence to low-phosphorus diets is difficult since phosphorus intake is directly linked to dietary protein intake and because such diets are often unpalatable.[61] As a result, most children treated with dialysis require phosphate-binding medications.

Phosphate-binding agents reduce intestinal phosphate absorption by forming poorly soluble complexes with phosphorus in the intestine. Aluminum-containing binders were frequently used in the past, but long-term treatment led to bone disease, encephalopathy, and anemia[62] and are currently used only in cases of severe hyperphosphatemia (> 7 mg/dl) associated with hypercalcemia.[62] When aluminum is necessary, citrate-containing compounds should be avoided, since citrate increases intestinal aluminum absorption[63] and increases the risk of acute aluminum intoxication.[64]

Calcium-containing salts are the mainstay in phosphorus-binding therapy. Several calcium salts are widely used, including calcium carbonate, calcium acetate, and calcium citrate. Calcium carbonate is the most commonly used compound.[65–67] Because of the increasing concern of vascular calcifications associated with a positive calcium balance due to high doses of vitamin D sterol and calcium-containing phosphate binders in the dialysis population, new non-aluminum, non-calcium-containing polymers, such as sevelamer hydrochloride (RenaGel®), show promise for future treatment of hyperphosphatemia in dialyzed children. These compounds are not yet approved for use in children, but sevelamer lowers serum phosphorus in children treated with dialysis[68] and has been shown to halt the progression of vascular calcifications in adult patients on hemodialysis while reducing LDL (low-density lipoprotein)- and raising HDL (high-density lipoprotein)-cholesterol.[69–72] This agent may, in the future, be beneficial, particularly in patients who are prone to developing hypercalcemia and in those requiring large doses of vitamin D. Lanthanum carbonate, another non-aluminum-, non-calcium-containing phosphate-binding agent, is a rare-earth metal that has been shown to effectively reduce serum phosphorus levels with fewer hypercalcemic episodes and a lower incidence of adynamic bone.[73–75] This agent is approved for use in the adult population but is not approved for use in children and has been shown to accumulate in the growth plate and liver of experimental animals, raising concern about its long-term safety in young patients.[76]

Vitamin D therapy

Treatment with vitamin D controls serum PTH levels and heals the changes of osteitis fibrosa. In children with low stores of 25(OH) vitamin D_3, supplementation with ergocalciferol or cholecalciferol may be sufficient to correct hyperparathyroidism and heal bony lesions. Some children have persistent elevation in PTH and bone turnover despite adequate vitamin D stores, and these children respond to treatment with active ($1,25(OH)_2D_3$) vitamin D sterol therapy. Care must be taken to avoid oversuppression of PTH in dialysis-dependent children, as adynamic bone may result in growth retardation.

Assessment and treatment of vitamin D deficiency

The liver synthesizes 25-hydroxyvitamin D ($25(OH)D_3$), the main storage form of vitamin D found in the body. Although 25-hydroxyvitamin D has not traditionally been considered to be the 'active' form of vitamin D, $25(OH)D_3$ has a substantial impact on bone physiology. Severe vitamin D deficiency (serum levels <5 ng/ml) with osteomalacia and hypocalcemia is rare, but vitamin D insufficiency (levels < 30 ng/ml) is prevalent in adults and is associated with increased PTH levels and fracture rates.[77–79] Although the prevalence of vitamin D deficiency in children is unknown, children with CKD are at risk for insufficiency due to urinary losses of vitamin D in proteinuric diseases and decreased sunlight exposure common in chronically ill children.

In contrast to the normal population, where $1,25(OH)_2D_3$ levels are maintained despite low stores of $25(OH)D_3$ levels,

$1,25(OH)_2D_3$ levels in patients with kidney disease fall proportionally with $25(OH)D_3$ levels. Levels of $1,25(OH)_2D_3$ may be dependent on the availability of substrate in mild to severe renal disease,[80] and modest supplementation with ergocalciferol ($25(OH)D_2$) or cholecalciferol ($25(OH)D_3$) in patients with insufficiency can lower PTH levels.[77,81] Ergocalciferol treatment should be initiated in patients with CKD when $25(OH)D_3$ levels fall below 30 ng/ml. Current pediatric dosing guidelines are based on degree of deficiency and are outlined in Table 23.3. Serum $25(OH)D_3$ levels should be rechecked after completion of the 3-month course of therapy.[82] Serum calcium and phosphorus levels should be measured after 1 month of therapy, then every 3 months, and supplementation discontinued if serum calcium levels exceed 10.2 mg/dl (2.54 mmol/L) or if serum $25(OH)D_3$ levels exceed 30 ng/ml.[82]

Treatment with vitamin D sterols

By increasing calcium absorption in the gut and by decreasing PTH gene transcription, active vitamin D sterols decrease PTH production. Treatment goals are aimed at decreasing PTH levels to the normal range for the stage of CKD, while avoiding hypercalcemia and hyperphosphatemia. Calcitriol (Rocaltrol®) is the most widely used sterol in children and has been shown to be equally effective when given in daily or intermittent oral doses.[54] When the dose is titrated to maintain normal PTH values in children with CKD, catch-up growth has been shown to occur.[53]

Due to the hypercalcemia associated with calcitriol and the importance of preventing vascular calcifications, new vitamin D analogues have been developed to minimize intestinal calcium and phosphorus absorption while effectively suppressing PTH. Three of these new vitamin D analogues are available for use in patients with chronic kidney disease: 22-oxacalcitriol (OCT) in Japan and 19-nor-1α-25-dihydroxyvitamin D_2 (paricalcitol) and 1α-hydroxyvitamin D_2 (doxercalciferol) in the USA. 19-nor-1α-25 dihydroxyvitamin D_2 (paricalcitol) is used in intravenous form and, compared with calcitriol, produces less hypercalcemia and results in greater survival rates in adults.[83] Doxercalciferol (an oral sterol) may have less calcemic effect than calcitriol in adults with CKD, although studies are needed to confirm the potential benefit in children.[84]

Treatment with calcimimetics

Cinacalcet, an allosteric activator of the calcium-sensing receptor, is now available for the treatment of secondary hyperparathyroidism in the adult dialysis population. By activating the calcium-sensing receptor, this small organic molecule is able to reduce PTH levels, decrease the calcium–phosphorus ion product,[85,86] and may provide a medical means of halting the progression of parathyroid gland hyperplasia.[87] This agent has not been approved for use in children, and due to the presence of the calcium-sensing receptor (CaSR) on the growth plate, studies are required to confirm the safety and efficacy in young patients.

Case presentation

A 12-year-old boy came to his pediatrician's office for a school physical. This was his first physical examination in several years. He stated that he had been feeling generally well, although he was perhaps sleeping more than usual and had to wake up several times at night to urinate. His family states that he had been healthy all his life, although he was much shorter than the rest of the other children in the family were at that age. The family history revealed no history of kidney disease or history of short stature. On examination, he was found to be a pale boy with a height and a weight that were both below the third percentile. He had Tanner 1 pubertal development, and normal blood pressure. There were no other abnormalities on physical examination.

The pediatrician obtained a radiographic bone age, serum chemistries, thyroid studies, and a urinalysis to evaluate his short stature. The patient was found to have sodium 136 mmol/L, potassium 3.8 mmol/L, chloride 108 mmol/L, total CO_2

Table 23.3 Dosing of ergocalciferol in vitamin D deficiency

Serum $25(OH)D_3$ (ng/ml)	Definition	Ergocalciferol dose	Duration	Comment
<5	Severe vitamin D deficiency	8000 IU/day orally × 4 weeks, then 4000 IU/day × 8 weeks	3 months	Measure $25(OH)D_3$ levels after 3 months
5–15	Mild vitamin D deficiency	4000 IU/day orally × 12 weeks	3 months	Measure $25(OH)D_3$ levels after 3 months
16–30	Vitamin D insufficiency	2000 IU/day orally × 12 weeks	3 months	

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18 mmol/L, blood urea nitrogen (BUN) 40 mg/dl, creatinine 1.8 mg/dl, phosphorus 4 mg/dl, calcium 8.6 mg/dl, albumin 3.2 g/dl, alkaline phosphatase 457 U/L, PTH 130 pg/ml, and a hematocrit 34%. Thyroid-stimulating hormone (TSH) was normal. The urinalysis revealed a specific gravity of 1.010, pH of 6, with no blood, protein, leukocyte esterase, nitrites, or glucose. A renal ultrasound showed bilaterally small kidneys with poor corticomedullary differentiation. The hand films revealed delayed bone age. The bones in the hand appeared abnormal, with subperiosteal erosion consistent with renal rickets.

Comment

Renal disease is high on the list of medical causes of short stature in a child with unexplained growth failure. Renal failure can cause short stature, and serum electrolytes, BUN, and creatinine, as well as a urinalysis, are crucial to evaluating for renal disease. A bone age will allow the clinician to evaluate for growth potential, as well as offering clues as to the etiology of the growth failure (a delayed bone age consistent with chronic illness, endocrinologic disorders, and constitutional growth delay).

Acidosis should be treated with bicarbonate therapy to increase serum bicarbonate levels to the normal range. A starting dose of 1 mEq of bicarbonate per kilogram of body weight per day should be initiated, and the dose titrated as needed to maintain normal serum bicarbonate levels.

A dietician who is knowledgable in nutrition in renal failure should follow the patient, ensuring that he maintains an appropriate (RDA-recommended) diet of protein and calories. In more advanced stages of CKD, nutritional guidance is also important in assuring restriction of phosphorus intake. Since renal phosphate excretion declines with decreasing renal function, children with advanced (stages 4 and 5) CKD must be made aware of foods that contain excessive amounts of phosphate. Dark sodas as well as dairy products should be avoided. Whereas meats are also high in phosphorus, an appropriate intake (1–1.5 g/kg/day) of protein is essential for adequate nutrition. Excess protein intake will also accompany excess phosphorus intake.

Although phosphate-binding agents are not required in this child, due to his normal serum phosphorus, as his kidney disease progresses and serum phosphorus levels rise, calcium carbonate may be used as a phosphate binder. Not only will it decrease serum phosphorus levels but it will also supply extra dietary calcium, which may become insufficient as ingestion of dairy products, which are high in phosphorus, are curtailed.

Active vitamin D sterol therapy, in the form of calcitriol, should be started to reduce PTH to levels appropriate for the stage of CKD. In this patient, with CKD stage 3, serum PTH levels should be targeted to between 35 and 70 pg/ml, since higher levels are associated with osteitis fibrosa at this degree of renal failure. If catch-up growth does not occur after correction of this child's hyperparathyroidism, growth hormone therapy should be initiated.

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24 Acute renal failure

Prasad Devarajan and Stuart L Goldstein

Acute renal failure (ARF), defined as a rapid decline in glomerular filtration rate (GFR), and leading to accumulation of nitrogenous wastes such as blood urea nitrogen (BUN) and creatinine, is a common problem afflicting all ages. ARF is associated with potentially serious consequences and unsatisfactory therapeutic options.[1–7] Oliguria occurs in less than half of cases. The etiology of ARF varies widely according to age, geographical region, and clinical setting. Prerenal azotemia resulting from dehydration is usually reversible with early therapy. Despite decades of research and technical advances in clinical care, the prognosis for patients with intrinsic ARF in the intensive care unit (ICU) setting remains poor. The cellular and molecular tools of modern science have provided critical new insights into the pathogenetic mechanisms of ARF. Novel strategies that modulate these pathways hold a considerable promise for the prevention and treatment of ARF.

Definitions

- **Acute renal failure:** a sudden, or rapid decline in renal function, irrespective of urine output.
- **Oliguria:** urine output less than 1 ml/kg/h in children, and less than 400 ml/day in adults.
- **Anuria:** complete cessation of urine output.

Classification

ARF may be classified as:

- prerenal azotemia, or functional response of structurally normal kidneys to hypoperfusion
- intrinsic ARF, resulting from structural damage to the renal parenchyma from prolonged ischemia, nephrotoxins, or glomerulonephritis
- postrenal ARF, arising from urinary tract obstruction.

Intrinsic ARF is morphologically associated with acute tubular necrosis (ATN). Consequently, it is common in clinical practice to interchangeably use the terms intrinsic ARF and ATN. Intrinsic ARF is frequently multifactorial in its origin, with concomitant ischemic, nephrotoxic, and septic components, and with overlapping pathogenetic mechanisms.

Epidemiology

Advancements in the care of critically ill neonates, infants with congenital heart disease, and children with bone marrow and solid organ transplantation has led to a dramatic broadening of the epidemiology of pediatric ARF. Although multicenter epidemiologic data on pediatric ARF do not exist, single-center data and literature reviews from the 1980s and 1990s report hemolytic uremic syndrome and other primary renal diseases as the most prevalent causes.[8–11] More recent single-center data have detailed the underlying causes of pediatric ARF in large cohorts of children. Bunchman et al reported congenital heart disease, ATN, sepsis, and bone marrow transplantation to be the most common etiologies in 226 children with ARF.[12] Another retrospective review of 248 patients, with a diagnosis of ARF on discharge or death, revealed ATN and nephrotoxins to be the most common causes of ARF.[13] Thus, the epidemiology of pediatric ARF has evolved in the developed countries from primary kidney diseases to secondary effects of other systemic illnesses or their treatment.

The precise incidence of pediatric ARF is not known, but appears to be rising, particularly in hospitalized children. For example, ARF complicates up to 24% of neonatal intensive care unit admissions, and is present in more than 60% of neonates with severe asphyxia.[10]

Prerenal azotemia

Prerenal ARF or azotemia is an appropriate functional response of structurally normal kidneys to hypoperfusion. The oliguria in this situation represents a renal mechanism for preserving intravascular volume. Prerenal azotemia is usually rapidly reversed by restoration of renal perfusion, but early treatment is essential in order to prevent the progression to intrinsic ARF. Table 24.1 lists the common causes of prerenal azotemia.

Pathophysiology

A decrease in circulatory volume evokes a systemic response aimed at normalizing intravascular volume at the expense of GFR. Baroreceptor-mediated activation of the sympathetic nervous system and renin–angiotensin axis results in renal vasoconstriction and the resultant reduction in GFR (Figure 24.1).

Table 24.1 Common causes of prerenal azotemia

Pathophysiologic mechanism	Etiology
Volume depletion	Dehydration Hemorrhage Diuretics Burns Shock Nephrotic syndrome Diabetes
Decreased cardiac output	Cardiac failure Arrhythmias
Peripheral vasodilatation	Sepsis Anaphylaxis Antihypertensives
Renal vasoconstriction	Sepsis Non-steroidal anti-inflammatory drugs ACE inhibitors Hepatorenal syndrome

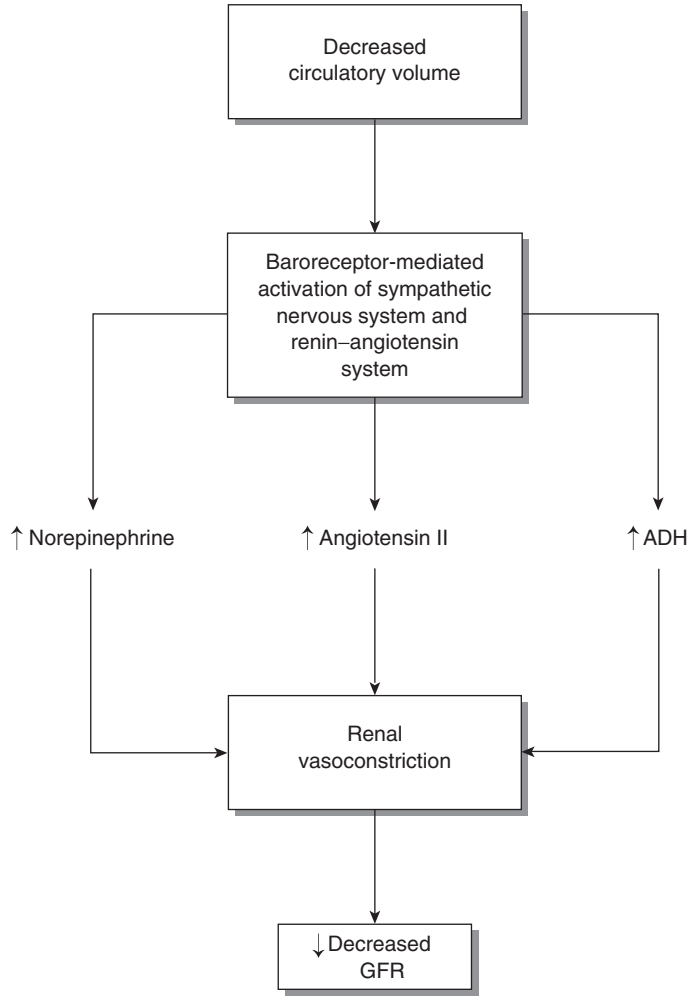

Figure 24.1 Pathophysiology of prerenal ARF.

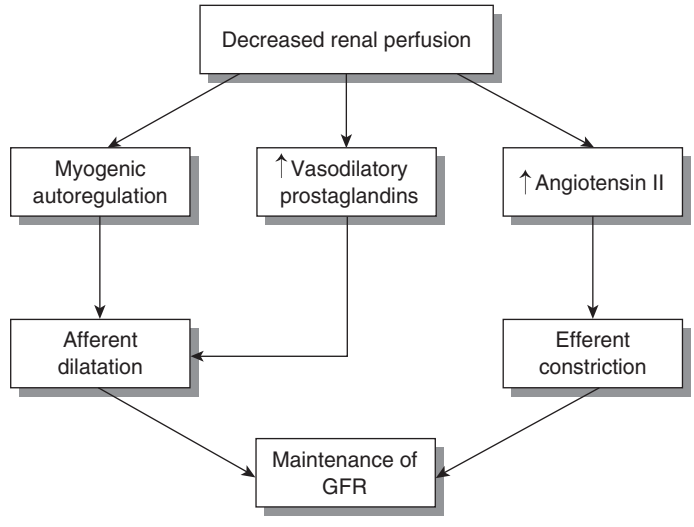

Figure 24.2 Renal compensatory mechanisms that maintain GFR in prerenal ARF. Iatrogenic interference with these mechanisms can precipitate a reduction in GFR.

However, several compensatory intrarenal mechanisms are brought into play in response to renal hypoperfusion, and these help to maintain GFR (Figure 24.2). Myogenic autoregulation refers to the unique ability of the afferent arterioles to rapidly vasodilate in response to a decrease in lateral stretch caused by hypoperfusion. The role of this response in hypoperfusion states has recently been challenged, and several investigators have suggested a more important role for autoregulation in maintaining intraglomerular pressure during systemic hypertension.[14] A more effective compensatory mechanism mediating afferent arteriolar dilatation involves the intrarenal generation of vasodilatory prostaglandins.[15] Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit this response and can precipitate ARF, especially in the presence of decreased circulatory volume.[16] A third mechanism involves the differential effect of angiotensin II on the efferent arteriole. While angiotensin II tends to constrict both the afferent and efferent arterioles, this effect is more marked in the efferent arteriole, leading to increased hydrostatic pressure across the glomerulus.[17] An interference with this compensatory mechanism can occur following angiotensin-converting enzyme inhibitor (ACEI) therapy. Prolonged reduction in renal perfusion pressure can overwhelm compensatory mechanisms that maintain GFR in prerenal azotemia, and intrinsic ARF can ensue.

Intrinsic acute renal failure

Intrinsic ARF is most frequently caused by prolonged ischemia or nephrotoxins (Table 24.2), and is associated pathologically with ATN. Consequently, it is common clinical practice to use

Table 24.2 Common causes of intrinsic acute renal failure

Pathophysiologic mechanism	Etiology
Acute tubular necrosis	Prolonged ischemia Nephrotoxins
Renal vascular diseases	Hemolytic uremic syndrome Vasculitides
Interstitial diseases	Interstitial nephritis Infections Infiltrations
Glomerulonephritides	Rapidly proliferative glomerulonephritis (RPGN) Membranoproliferative glomerulonephritis (MPGN) Postinfectious glomerulonephritis

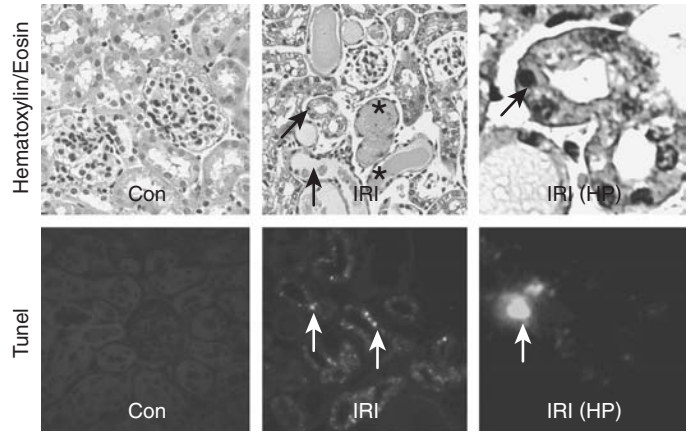

Figure 24.3 Morphology of ATN. Sections from control (Con) and ischemia–reperfusion injury (IRI) kidneys stained with hematoxylin–eosin (top panel) to reveal general morphology. Arrows show apoptotic cells and asterisks (*) represent a dilated tubule with flattened epithelium and intratubular cast formation. The bottom panel shows dUTP-biotin nick end labeling (TUNEL) technique to illustrate apoptotic cells (arrows). HP = high power.

the terms intrinsic ARF and ATN interchangeably. In the clinical setting, intrinsic ARF is frequently multifactorial, with concomitant ischemic, nephrotoxic, and septic components, and with overlapping pathogenetic mechanisms.

Morphology of ATN

ATN is a misnomer, since frank tubular cell necrosis is rarely found in human ARF. Instead, there is effacement and loss of proximal tubule brush border, patchy loss of tubular cells, focal proximal tubular dilatation and distal tubular casts, and areas of cellular regeneration, as shown in Figure 24.3. Necrotic cell death is restricted to the outer medullary regions (S3 segment of the proximal tubule and medullary thick ascending limb of Henle's loop). More recently, apoptosis has been reported in both distal and proximal tubules, in both ischemic and nephrotoxic forms of human ARF.[18,19] In addition, peritubular capillaries in the outer medulla have been shown to display a striking vascular congestion and leukocyte accumulation.[20–24]

Hemodynamic alterations

Total renal blood flow is reduced to about 50% of normal due to persistent intense renal vasoconstriction in established ATN, by mechanisms shown in Figure 24.4.[3] Furthermore, there is evidence for regional alterations in renal blood flow, with marked congestion of the outer medullary region.[20–24] Oxygen tensions are normally low in this region, which contains tubular segments with high energy requirements: namely, the S3 segment of the proximal tubule and medullary thick ascending limb. The post-ischemic congestion worsens the relative hypoxia, leading to prolonged injury and necrotic cell death in these segments. Mechanisms underlying these hemodynamic alterations relate primarily to endothelial damage.[22–24] This leads to a local imbalance of vasoactive substances, including enhanced release of the vasoconstrictor endothelin and reduced release of vasodilatory endothelium-derived nitric oxide.[3] Endothelin receptor antagonists ameliorate ischemic ARF in animals,[25] but human data are lacking. Nonetheless, these hemodynamic abnormalities cannot fully account for the profound loss of renal function, and several human trials of vasodilators such as dopamine have failed to demonstrate improvement in GFR in established ATN despite augmentation of renal blood flow.[26]

Alterations in tubular dynamics

Three well-known alterations in tubular dynamics in ATN are obstruction, back-leak, and activation of tubuloglomerular feedback.[3] Their interplay is illustrated in Figure 24.4. The consistent finding of proximal tubular dilatation and distal tubular casts in human ARF are indicative of obstruction to tubular fluid flow. The intraluminal casts stain strongly for Tamm–Horsfall protein, which is normally secreted by the thick ascending limb as a monomer. Conversion into a gel-like polymer is enhanced by the increased luminal sodium concentration typically encountered in the distal tubule in ATN.[27] This provides an ideal environment for cast formation along with desquamated tubule cells and brush border membranes. However, it is unlikely that obstruction alone can account for the profound dysfunction in clinical ATN, since human studies using forced diuresis with furosemide[28] or mannitol[29] did not impact on the survival and renal recovery rate of patients with established ARF. Similarly, although movement of the glomerular filtrate back into the circulation has been shown to occur, this accounts for only a very minor component of the decrease in GFR in

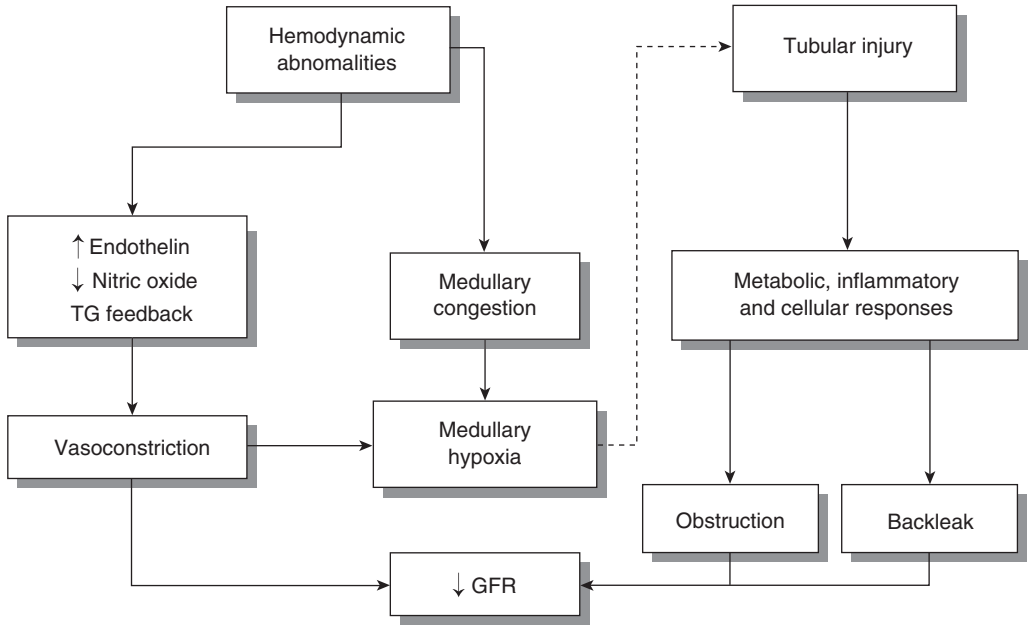

Figure 24.4 Pathophysiology of intrinsic ARF.

human ATN.[3] Finally, a role for activation of tubuloglomerular feedback has been proposed.[30] The increased delivery of sodium chloride to the macula densa due to abnormalities in the ischemic proximal tubule would be expected to induce afferent arteriolar constriction via A1 adenosine receptor (A1AR) activation, and thereby decrease GFR.[31] However, a knockout of the A1AR results in a paradoxical worsening of ischemic renal injury, and exogenous activation of A1AR was protective.[32] Thus, tubuloglomerular feedback activation following ischemic injury may represent a beneficial phenomenon that limits wasteful delivery of ions and solutes to the damaged tubules.

Alterations in tubular cell metabolism

A profound reduction in intracellular ATP content occurs early after ischemic renal injury, which triggers a number of metabolic consequences in tubule cells.[33] These events are detailed below, and their interrelationship is illustrated in Figure 24.5.

Alterations in adenine nucleotide metabolism have been well documented. Oxygen deprivation leads to a rapid degradation of ATP to AMP and to hypoxanthine. These metabolites are freely diffusible, and their depletion precludes resynthesis of ATP during reperfusion. Provision of exogenous adenine nucleotides or thyroxine (which stimulates mitochondrial ATP regeneration) can ameliorate the cellular injury in animal models of ischemic ARF, but has proven ineffective in established human ATN.[34] An increase in free intracellular calcium has also been documented following ATN, but the role has remained controversial. Increased intracellular calcium could potentially lead to activation of proteases and phospholipases. A recent meta-analysis suggests that calcium channel blockers may provide some protection from renal injury in the transplant setting,[35] but evidence for their efficacy in other forms of ARF is lacking.

There is now substantial evidence for the role of reactive oxygen species in the pathogenesis of ATN. During reperfusion, the conversion of accumulated hypoxanthine to xanthine generates hydrogen peroxide and superoxide. In the presence of iron, hydrogen peroxide forms the highly reactive hydroxyl radical. Concomitantly, ischemia induces nitric oxide synthase in tubule cells, and the nitric oxide generated interacts with superoxide to form peroxynitrate, which results in cell damage via oxidant injury as well as protein nitrosylation.[33] A recent landmark study has documented a dramatic increase in oxidative stress in adults with ARF.[36] Several scavengers of reactive oxygen molecules protect against ischemic ATN in animals, but human studies have been inconclusive. A promising new advance in the field is the protective effect of the free radical scavenger edaravone in a rat model of ischemic ARF.[37] Edaravone has been approved for human use in the treatment of cerebral ischemia. Also, the iron scavenger deferoxamine ameliorates ischemia–reperfusion injury in animal models, but the associated toxicity precludes its clinical use in human ARF. Two major advances have recently emerged in the area of iron chelation. The first advance is the availability of human apotransferrin, an iron-binding protein, which protects against renal ischemia–reperfusion injury in animals by abrogating renal superoxide formation.[38] The second advance is the discovery of neutrophil gelatinase-associated lipocalin (NGAL), an endogenous iron-transporting protein, as one of the most highly induced genes and proteins in the kidney following early ischemic injury.[39] Administration of NGAL provides significant functional protection in an animal model of ARF.[40]

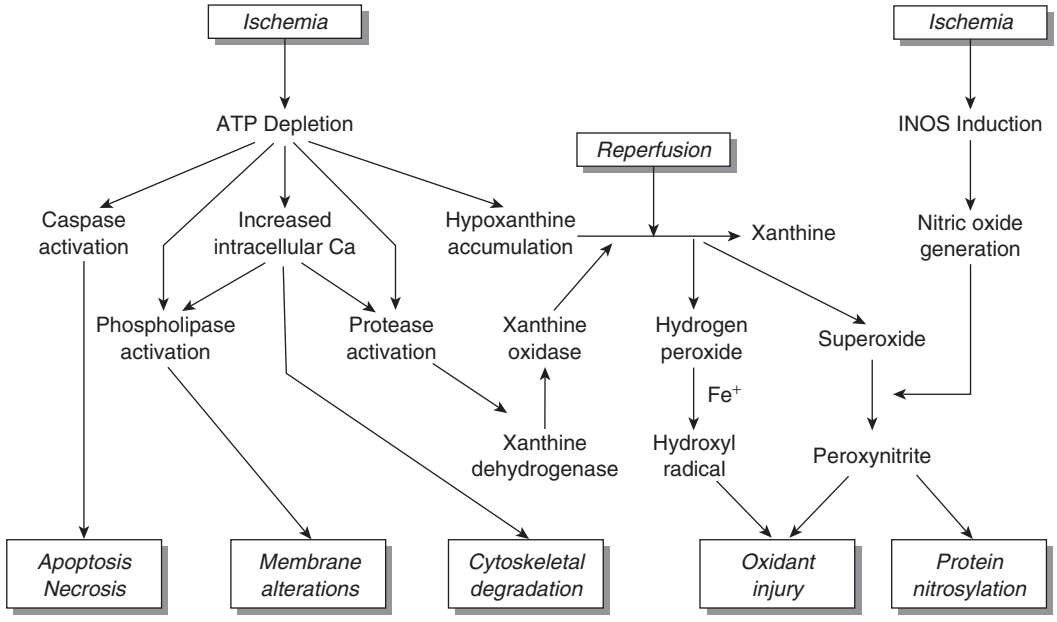

Figure 24.5 Metabolic consequences of acute ischemia and reperfusion injury to kidney tubule cells. Inhibition of these pathways may provide novel therapeutic approaches to ARF. INOS, Inducible Nitric Oxide Synthase. Adapted from reference 1, with permission.

The potential use of both of these endogenous agents in human ARF is currently under investigation.

Alterations in tubular cell structure

The biologic response of the tubular cell to ischemia is multifaceted, and includes loss of cell polarity and brush borders, cell death, dedifferentiation of viable cells, proliferation, and restitution of a normal epithelium, as illustrated in Figure 24.6. The mechanisms underlying this morphologic sequence of events are examined below.

Ischemia results in a rapid disruption of the apical actin cytoskeleton and redistribution of actin from the apical domain and microvilli into the cytoplasm.[41] This results in loss of brush border membranes, which contributes to cast formation and obstruction. Disruption of the apical cytoskeleton also results in loss of tight junctions and occludens junctions (which accounts for the back-leak of glomerular filtrate).

Ischemia results in the early disruption of at least two basolaterally polarized proteins, namely Na/K-ATPase and integrins. The Na/K-ATPase is normally tethered to the spectrin-based cytoskeleton at the basolateral domain via the adapter protein ankyrin. This provides the driving force for the normal reabsorption of salt and water by the proximal tubule. Ischemia leads to a reversible cytoplasmic accumulation of Na/K-ATPase, ankyrin, and spectrin in viable cells.[42] Postulated mechanisms leading to loss of Na/K-ATPase polarity include disruption of the cortical actin cytoskeleton and cleavage of spectrin by ischemia-induced activation of proteases such as calpain.[3] The physiologic consequence is the impaired proximal tubular sodium reabsorption that is characteristic of intrinsic ARF. The β_1-integrins are normally polarized to the basal domain, where they mediate cell–substratum adhesions. Ischemic injury leads to a redistribution of integrins to the apical membrane, with consequential detachment of viable cells from the basement membrane. There is good evidence to indicate abnormal adhesion between these exfoliated cells within the tubular lumen, mediated by an interaction between apical integrin and the Arg–Gly–Asp (RGD) motif of integrin receptors.[43] Administration of synthetic RGD compounds attenuates tubular obstruction and renal impairment in animal models of ischemic ATN.

Ischemic renal injury leads to tubular cell death by at least two pathophysiologic mechanisms.[44] Necrosis is characterized by loss of membrane integrity, cytoplasmic swelling, nuclear pyknosis, cellular fragmentation, and an inflammatory response. Apoptosis is characterized by cytoplasmic and nuclear shrinkage, DNA fragmentation, and breakdown of the cell into apoptotic bodies that are rapidly removed by phagocytosis. These two forms of cell death frequently coexist, and are two extremes of a continuum. Following ischemic renal injury, the mode of cell death depends primarily on the severity of the insult and the resistance of the cell type. Necrosis occurs following more severe injury and in the more susceptible proximal tubules, whereas apoptosis predominates after less severe injury and especially in the ischemia-resistant distal nephron segments. Mounting evidence now indicates that apoptosis is a major mechanism of early tubule cell death in both animal[44–47] and human[9,48–53] models of ATN, as illustrated in Figure 24.3. Considerable attention has recently been directed towards unraveling the molecular pathways involved in renal tubular cell apoptosis. Multiple pathways, including the intrinsic (Bcl-2 family, cytochrome c, caspase 9), extrinsic (Fas, FADD, caspase 8) and regulatory (p53) factors appear to be activated by

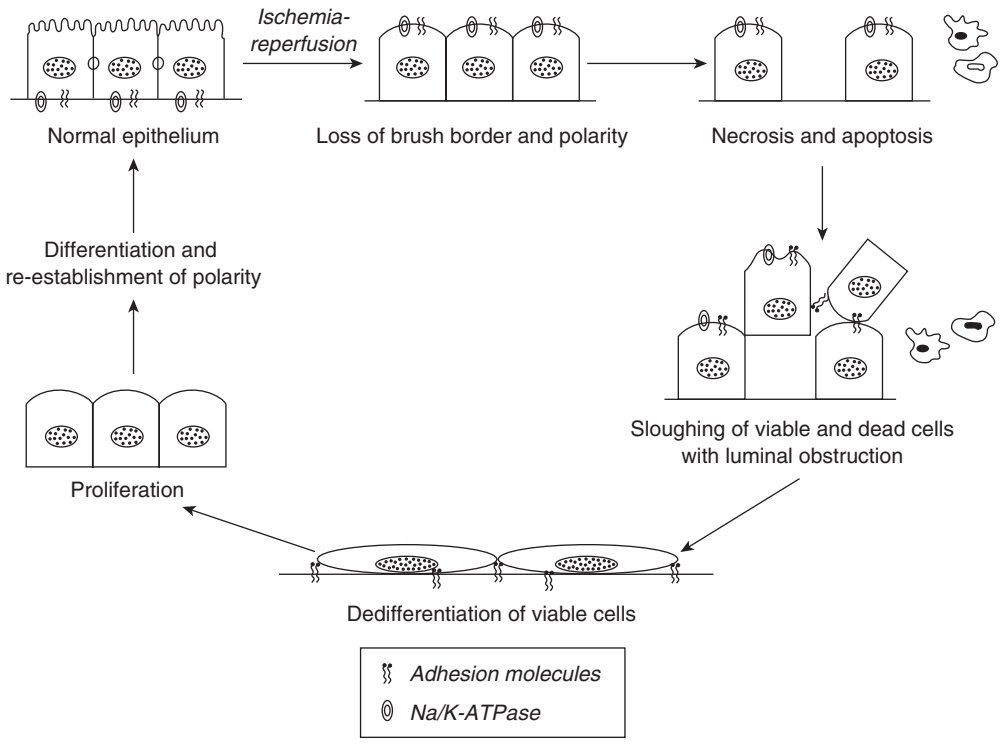

Figure 24.6 Schematic representation of consequences of acute ischemia and reperfusion injury to kidney tubule cells. Novel therapeutic approaches in ARF have targeted prevention of cell death and acceleration of the endogenous recovery process. Adapted from reference 1, with permission.

ischemic renal injury, as illustrated in Figure 24.7.[1,53] Inhibition of apoptosis holds promise in ischemic ARF. However, current inhibitory maneuvers have only been investigated in animals, provide only partial functional protection, and are most effective when administered before the injury.

Renal tubular cells possess a remarkable ability to regenerate and proliferate after ischemic injury.[54] Morphologically, repair is heralded by the appearance of dedifferentiated tubule cells.[54] In the next phase, the cells upregulate genes encoding for a variety of growth factors such as IGF-1 (insulin-like growth factor 1), HGF (hepatocyte growth factor), and FGF (fibroblast growth factor), and undergo marked proliferation. In the final phase, cells undergo redifferentiation until the normal fully polarized epithelium is restored. Thus, during recovery from ischemia, renal tubule cells recapitulate processes similar to those during normal kidney development.[53–55] Understanding the molecular mechanisms of repair may provide clues towards accelerating recovery from ARF. The potential use of progenitor cells and stem cells as therapeutic strategies in ARF is currently under initial stages of investigation.[56,57]

Role of the inflammatory response

There is now increasing evidence in animal and human studies for a role of inflammation in the pathogenesis of ischemic ARF.[20,21] The major components of this response include endothelial injury, leukocyte recruitment, and production of inflammatory mediators by tubular cells. The endothelial injury is manifested by endothelial swelling, narrowing of the blood vessels, abnormal retrograde blood flow upon reperfusion, and the induction of adhesion molecules such as ICAM-1 (intercellular adhesion molecule 1) and P-selectin that promote endothelial–leukocyte interactions. Although ablation of the *ICAM-1* gene and pretreatment with ICAM-1 antibody rendered mice resistant to ischemic ARF, human trials with anti-ICAM-1 antibody did not prevent ATN in cadaveric transplant recipients. Morphologically, both neutrophils and T cells have been shown to aggregate in peritubular capillaries following ischemic ATN in humans, and the relative roles of these leukocyte subtypes remains under investigation. The ischemic proximal tubular epithelium can generate a number of mediators that potentiate the inflammatory response. These include cytokines such as TNF-α (tumor necrosis factor α), interleukins IL-6 and IL-1β, and chemotactic cytokines (MCP-1, IL-8, RANTES). Recent studies have shown that the plasma levels of the pro-inflammatory cytokines IL-6 and IL-8 predict mortality in adults with ARF.[58] Strategies that modulate the inflammatory response may provide significant beneficial effects in human ARF.

Postrenal acute renal failure

Postrenal ARF is a result of obstruction to the outflow tract on both sides, and is uncommon beyond the neonatal period.

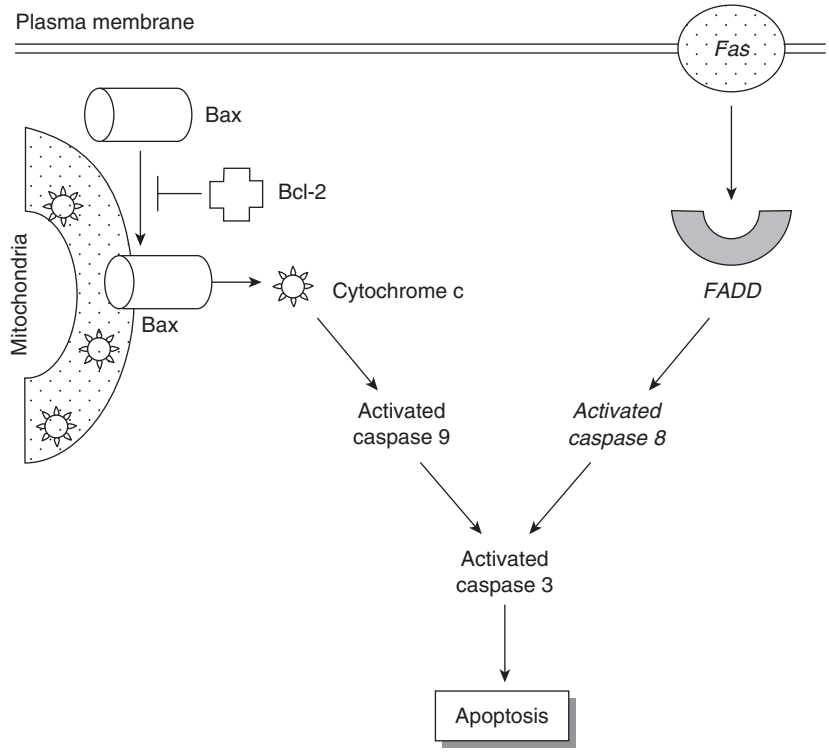

Figure 24.7 Major apoptotic pathways induced by acute ischemia and reperfusion injury to human kidney tubular cells. The extrinsic pathway (*italics*) requires activation of plasma membrane Fas receptor, with signal transduction via FADD resulting in activation of caspase 8. The intrinsic pathway requires translocation of Bax (which is normally prevented by Bcl-2) to the mitochondria, thereby forming pores for the release of cytochrome c and activation of caspase 9. Bax is also activated by p53-dependent pathways (not shown). Both caspase 8 and 9 activate caspase 3, which initiates the morphologic cascades of apoptosis. Inhibition of these pathways holds significant therapeutic promise in human ARF. Adapted from reference 1, with permission.

Postrenal azotemia is usually reversed by relief of the obstruction, but is accompanied by a very significant postobstructive diuresis. The common causes of postrenal ARF are listed in Table 24.3. The pathophysiology and management of the obstructive uropathy syndrome that can result from congenital obstruction are detailed in Chapter 32.

Table 24.3 Common causes of postrenal acute renal failure

Mechanism	Etiology
Congenital	Urethral valves Ureteropelvic junction obstruction
Acquired	Calculi Clots Neurogenic bladder Drugs that cause urinary retention Extrmsic compression by tumors

Clinical presentation of acute renal failure

ARF most commonly presents with a progressive accumulation of nitrogenous wastes in a predisposed patient. Less frequently, one encounters an unexplained rise in BUN and creatinine, and the evaluation of such patients requires a complete history, physical examination, review of medical records and drug history, laboratory evaluation, renal imaging, and rarely a kidney biopsy. The assessment is directed towards

- identifying the underlying cause
- distinguishing between prerenal and intrinsic ARF
- discriminating between ARF and *chronic renal failure (CRF)*.

Identifying the underlying cause

Salient aspects of the ARF history and physical examination are shown in Tables 24.4 and 24.5 respectively. These, in combination with a detailed urinalysis, will yield the etiology of ARF in the majority of cases. Typically, the urine in prerenal azotemia contains only a few hyaline and fine granular casts, with little protein or blood. In contrast, proteinuria and hematuria are prominent in intrinsic ARF. A heme-positive urine in the absence of red blood cells (RBCs) in the sediment

Table 24.4 Relevant history in patients with suspected acute renal failure

Fluid loss:
- Diarrhea, vomiting
- Burns
- Surgery, shock

Nephrotoxic agents:
- Non-steroidal anti-inflammatory drugs
- Aminoglycosides
- Contrast agents

Glomerular disease:
- Streptococcal infection (poststreptococcal glomerulonephritis)
- Bloody diarrhea (hemolytic uremic syndrome)
- Fever, joint complaints, rash (systemic lupus erythematosus)

Obstruction:
- Complete anuria
- Poor urinary stream

Table 24.5 Relevant physical signs in acute renal failure

Clinical sign	Diagnostic interpretation
Signs of intravascular volume depletion	Prerenal azotemia
Edema, hypertension	Fluid overload
Signs of underlying renal disease:	
• Butterfly rash, joint swelling	Systemic lupus erythematosus
• Purpuric rash	Henoch–Schönlein purpura, vasculitis
• Fever, macular rash	Interstitial nephritis
• Palpably enlarged kidneys	Bilateral urinary tract obstruction, polycystic, multicystic kidney disease, renal vein thrombosis
Signs of urinary obstruction: • Poor urinary stream • Palpably enlarged bladder • Therapeutic catheterization	Bladder outlet obstruction

suggests hemolysis or rhabdomyolysis. Urine microscopy reveals dysmorphic RBCs in glomerular disease, and white blood cells (WBCs) in pyelonephritis or interstitial nephritis. Broad brown granular casts are typically encountered in ischemic or toxic ATN, whereas RBC casts are characteristic of acute glomerulonephritis and WBC casts indicate interstitial nephritis or pyelonephritis.

Distinguishing between prerenal and intrinsic ARF

This distinction is based on the principle that prerenal azotemia is associated with maximal reabsorption of solutes and water by the intact proximal tubule, whereas the tubule cell damage typical of intrinsic ARF results in impaired reabsorptive capacity of the proximal tubule. Urinary indices based on this principle are shown in Table 24.6: the fractional excretion of sodium (FENa) has been reported to be the most accurate factor for making this distinction. It is calculated from measured concentrations of sodium (Na) and creatinine (Cr) in the urine (U) and plasma (P), as follows:

$$\text{FENa} = ([\text{U/P}]\text{Na})/([\text{U/P}]\text{Cr}) \times 100$$

Interpretation of these indices must take into account any abnormal presence of substances in the urine such as protein, glucose, mannitol, contrast agents, and diuretic therapy. By the same principle of increased solute reabsorption, the BUN/creatinine ratio in the serum is markedly elevated (>20) in prerenal azotemia.

Table 24.6 Urinary indices in acute renal failure

Test	Prerenal ARF	Intrinsic ARF
Urine specific gravity	> 1,020	< 1,012
Urine/plasma creatinine	> 40	< 20
Urine Na (mEq/L)	< 20	> 40
FENa	< 1%	> 2%

Distinguishing between ARF and CRF

A kidney and bladder ultrasound is a sensitive, non-invasive modality that can differentiate not only between ARF and CRF but can also rule out a postrenal etiology. Typically, the kidneys in ARF are normal or enlarged, with increased echogenicity, whereas those in CRF are frequently small and shrunken. Other distinguishing features are shown in Table 24.7.

Problems with serum creatinine measurements in ARF

An increase in serum creatinine (1–1.5 mg/dl/day) and BUN (10–20 mg/dl/day) has been considered as the hallmark of ARF. However, determination of a practical ARF definition to guide

Table 24.7 Clinical and investigative tools differentiating acute renal failure from chronic renal failure

Acute renal failure	Chronic renal failure
Progressive rise in BUN and Cr	Stable elevated BUN and Cr
History of ARF etiology	History of chronic hypertension
Normal growth	Stunted growth
Normal bones	Renal osteodystrophy
No broad urinary casts	Broad waxy urinary casts
Anemia usually mild	Anemia usually severe
Normal or enlarged kidneys	Small shrunken kidneys

patient management has been hampered by reliance on serum creatinine as the primary marker of renal function.[59] Serum creatinine concentration is a less than ideal ARF marker for several reasons:

- it does not differentiate the nature, type, and timing of the renal insult
- changes in serum creatinine concentrations often lag behind changes in GFR until a steady state has been reached
- dialysis readily clears serum creatinine, rendering serum creatinine levels useless in the assessment for improving renal function once dialysis has begun
- serum creatinine varies widely with age, gender, diet, and hydration status.

Recently, a consensus conference of nephrologists and intensivists has proposed a multidimensional ARF definition based on differing degrees of GFR and urine output changes, termed the RIFLE (Risk, Injury, Failure, Loss and ESRD) criteria.[6] Use of such clinical criteria will be helpful to standardize the definition of acute renal failure, to guide decisions to initiate and terminate renal replacement therapy for patients with ARF, and to refine the epidemiology of ARF.

Complications of acute renal failure

ARF is associated with a number of life-threatening complications, which the clinician must constantly be diligent about. Common complications are listed in Table 24.8.

Hyponatremia is a common laboratory finding and usually dilutional (secondary to fluid retention and administration of hypotonic fluids). Less common causes of hyponatremia include sodium depletion (hyponatremic dehydration) and hyperglycemia (serum sodium concentration decreases by 1.6 mEq/L for every 100 mg/dl increase in serum glucose above 100 mg/dl). Hypernatremia in ARF is usually a result of excessive sodium administration (inappropriate fluid therapy or overzealous sodium bicarbonate administration).

Hyperkalemia is due to the reduction in GFR, reduction in tubular secretion, increased catabolism, and metabolic acidosis (each 0.1 unit reduction in arterial pH raises serum potassium by 0.3 mEq/L). Hyperkalemia is most pronounced in patients with excessive endogenous production (rhabdomyolysis, hemolysis, and tumor lysis syndrome). Symptoms are non-specific and may include malaise, nausea, and muscle weakness. Electrocardiographic (ECG) changes should be looked for in all patients suspected of having hyperkalemia, including (in sequence according to the severity of hyperkalemia) tall peaked T waves, prolonged PR interval, flattened P waves, widened QRS complex, ventricular tachycardia, and fibrillation.

A high anion gap metabolic acidosis is common, and is secondary to the impaired renal excretion of acids and the impaired reabsorption and regeneration of bicarbonate. Acidosis is most severe in shock, sepsis, or impaired respiratory compensation.

Hypocalcemia is commonly encountered in ARF, and is due to increased serum phosphate and impaired renal conversion of vitamin D to the active form. Hypocalcemia is most pronounced in patients with rhabdomyolysis. Metabolic acidosis increases the fraction of ionized calcium (the active form). Therefore, overzealous bicarbonate therapy can decrease the concentration of ionized calcium and precipitate symptoms of hypocalcemia, including tetany, seizures and cardiac arrhythmias. Hyperphosphatemia is primarily due to impaired renal excretion, and can aggravate the hypocalcemia.

Table 24.8 Complications of acute renal failure

Metabolic	Cardiovascular	Gastrointestinal	Neurologic	Hematologic	Infectious
Hyperkalemia	Pulmonary edema	Nausea, vomiting, anorexia	Altered mental status	Anemia	Pneumonia
Metabolic acidosis	Arrhythmias	Malnutrition	Irritability	Bleeding	Sepsis
Hyponatremia	Pericarditis	Gastritis	Seizures		Infected IV sites
Hypocalcemia	Myocardial infarction	GI bleeding	Somnolence		
Hyperphosphatemia	Hypertension	GI ulcers	Coma		

The genesis of non-renal complications is complex, and ARF per se is a major risk factor for their development. The accumulation of unidentified 'uremic toxins' is postulated to play a major role in the cardiac, gastrointestinal, and neuropsychiatric disturbances. During recovery from ARF, the vigorous diuretic phase may be accompanied by significant volume depletion, hypernatremia, hypokalemia, and hypophosphatemia.

Management of acute renal failure

Fluids, electrolytes, and nutrition

ARF associated with intravascular volume depletion requires prompt and vigorous fluid resuscitation with normal saline (20 ml/kg over 30–60 minutes, repeated twice if necessary). This should result in urine output within about 4 hours; if not, the bladder should be catheterized to confirm anuria. Potassium is contraindicated until urine flow is well established and the serum potassium begins to normalize. Patients who are oliguric should be provided with fluids to equal insensible water loss plus replacement of output. Oliguria with fluid overload is managed with fluid restriction and diuretics. Resistance to diuretics (typical of ATN) may necessitate dialysis. Aggressive nutritional support is crucial to enhance the recovery process. Adequate calories to account for maintenance requirements and supplemental calories to combat excessive catabolism should be administered by oral, enteral, or parenteral routes as appropriate. If adequate nutrition cannot be achieved because of fluid restriction, early institution of dialysis should be strongly considered.

The management of hyperkalemia deserves special mention, and is detailed in Table 24.9. Mild to moderate hyperkalemia (serum potassium of 5.5–6.5 mmol/L) is treated by eliminating all sources of potassium from the diet or IV fluids, and administration of an ion exchange resin such as sodium polystyrene sulfonate. This therapy requires several hours of contact with the colonic mucosa to be effective. Emergency treatment is indicated when the serum potassium exceeds 6.5 mmol/L or if any ECG changes are present. In addition to ion exchange resin, such patients should emergently receive calcium gluconate to counteract the effects of hyperkalemia on the myocardium. Uptake of potassium by cells should be stimulated by infusion of glucose and insulin (in the absence of significant fluid overload), the β-agonist albuterol by nebulizer, and sodium bicarbonate. Overzealous use of bicarbonate therapy in ARF can precipitate hypocalcemia and hypernatremia, and bicarbonate administration is currently advocated only in the presence of significant metabolic acidosis. In practice, the definitive therapy for significant hyperkalemia in oliguric ARF is dialysis, and the non-dialytic therapy outlined above serves mostly to tide over the acute crisis.

Medications

Nephrotoxic agents should be avoided in ARF as they may worsen the injury and delay recovery of function. The dose of all medications should be adjusted based on residual renal function. However, patients with ARF even in the early phase with a rising creatinine should be assumed to have a GFR of < 10 ml/min, irrespective of the absolute value of the serum creatinine.

Renal replacement therapy

The common indications for acute dialytic therapy in ARF include:

- fluid overload that is unresponsive to diuretics or is a hindrance to adequate nutrition
- hyperkalemia that is unresponsive to non-dialytic therapy
- refractory hypertension
- symptomatic uremia, including pericarditis, pleuritis, and neurologic symptoms.

The choices available include hemodialysis (HD), peritoneal dialysis (PD), and continuous renal replacement therapy (CRRT). These modalities are described in detail in other chapters of this book, and only general comments pertaining to ARF are included here. The choice of dialysis modality

Table 24.9 Non-dialytic treatment of hyperkalemia

Agent	Mechanism	Dose	Onset of action
Sodium polystyrene sulfonate	Exchanges Na^+ for K^+ across colonic mucosa	1 g/kg PO or PR with sorbitol	1–2 hours
Calcium gluconate	Stabilizes the myocardial membrane potential	1 ml/kg IV over 5–15 minutes	Immediate
Glucose and insulin	Stimulates cellular uptake of K^+	Glucose 0.5 g/kg, insulin 0.1 units/kg over 30 minutes	30 minutes
β-agonists (albuterol)	Stimulates cellular uptake of K^+	5–10 mg dose by nebulizer	30 minutes
Sodium bicarbonate	Shifts K^+ into cells	1 mmol/kg IV over 10 minutes	15 minutes

depends on the clinical status of the patient, the expertise of the physician, and the availability of appropriate resources. Hemodialysis requires central vascular access, specialized equipment and technical personnel, anticoagulation (except in patients with coagulopathy), and the ability to tolerate a large extracorporeal volume. Critically ill patients frequently require pressor support for effective hemodialysis. The advantage of hemodialysis in the setting of ARF lies in its ability to rapidly correct imbalances in fluid, electrolyte, and acid–base status. The use of biocompatible dialyzer membranes such as polysulfone has been associated with an improved outcome in many[61] but not all[62] studies. The advantages of PD include ease of performance, and no requirement for specialized equipment, personnel, or systemic anticoagulation. It is frequently the therapy of choice in neonates and small infants.

Transition from the use of adaptive CRRT equipment[63] to production of hemofiltration machines with volumetric control allowing for accurate ultrafiltration flows has led to a change in pediatric renal replacement therapy modality patterns.[64] Accurate ultrafiltration and blood flow rates are crucial for pediatric CRRT, since the extracorporeal circuit volume can comprise more than 15% of a small pediatric patient's total blood volume and small inaccuracies in ultrafiltration may represent a large percentage of the patient's total body water. Polls of US pediatric nephrologists demonstrate increased CRRT use over peritoneal dialysis as the preferred modality for treating pediatric ARF.[65,66] CRRT is especially useful in the presence of hemodynamic instability and multi-organ dysfunction, since it allows for gentle, continuous management of fluid overload.

Special considerations

The critically ill pediatric patient

As opposed to adults, children tend to develop severe and life-threatening multi-organ dysfunction syndrome very early in their ICU course. Methods to identify patients at risk and aggressive initiation of supportive measures such as CRRT could conceivably improve the outcome. For example, children who receive CRRT and have a requirement for pressor support display a higher mortality than those who do not need pressors in the course of their ARF treatment.[12] More recent data demonstrate that worsening fluid overload is an independent risk factor for mortality in critically ill children who receive CRRT, irrespective of the severity of illness.[67,68] These results suggest that early initiation of CRRT at lesser degrees of fluid overload may allow for more optimal nutrition and blood product provision without the further accumulation of fluid or catabolic waste products, thereby improving the outcome.

Infants

Infants and neonates with ARF present unique problems for renal replacement therapy provision. Delivery of hemodialysis or CRRT entails a significant portion of their blood volume to be pumped through the extracorporeal circuit. Therefore, extracorporeal circuit volumes that comprise more than 10–15% of patient's blood volume should be primed with whole blood to prevent hypotension and anemia. Since the prime volume is not discarded, it is important to not re-infuse the blood into the patient at the end of the treatment in order to prevent volume overload and hypertension. Acute peritoneal dialysis requires much less technical expertise, expense, and equipment compared with intermittent hemodialysis and CRRT. PD catheters can be placed quickly and easily. Initial dwell volumes should be limited to 10 ml/kg of patient body weight in order to minimize intra-abdominal pressure and potential for fluid leakage along the catheter tunnel. Although PD may deliver less efficient solute removal than hemodialysis or CRRT, its relative simplicity and minimal associated side effects allow for renal replacement therapy provision in settings lacking pediatric dialysis specific support and personnel. CRRT has been prescribed since the mid-1980s for treatment of ARF in critically ill infants. A recent evaluation of the CVVH (continuous venovenous hemofiltration) course for 90 infants less than 10 kg demonstrated very few technical complications using newer CVVH machinery.[69] Survival for infants receiving CRRT has been noted to be at 35–38%, which is similar to survival rates for older children, although patients < 3 kg exhibit a trend towards worse survival when compared with larger infants.[69]

Congenital heart disease

The incidence of ARF after cardiopulmonary bypass (CPB) in infants ranges from 2.7% to 5.3%, with survival rates ranging from 21% to 70%.[70] Risk factors for mortality include increasing underlying complexity of the congenital heart disease and poor cardiac function. A recent trend toward providing PD therapy earlier in the post-CPB course has been reported, with one study of 20 patients demonstrating 80% patient survival.[71] Improved survival with early PD initiation may result from prevention of fluid overload, and from increased clearance of CPB-induced proinflammatory cytokines. Some institutions have advocated the prophylactic use of PD immediately postoperatively in order to prevent fluid accumulation in patients with high-risk underlying diagnoses such as hypoplastic left heart syndrome, transposition of the great arteries, or anomalous pulmonary venous return.

Outcome and prognosis in acute renal failure

Children who 'recover' from ARF secondary to hemolytic uremic syndrome exhibit a 10–25% rate of progression to chronic renal insufficiency or end-stage renal failure.[71] Long-term follow-up of premature infants with neonatal ARF has shown a 45% rate of renal insufficiency.[72] Prominent risk factors for progression include an increased random urine protein/creatinine ratio and a serum creatinine > 0.6 mg/dl at 1 year of age.[72] A preliminary analysis of the cohort of ARF

patients from Texas Children's Hospital has revealed a significant rate of chronic renal insufficiency, hyperfiltration, and microalbuminuria during a 3–5 year-follow-up. Collectively, these data strongly suggest that long-term follow-up is warranted for children who survive an ARF episode.

Prevention of acute renal failure

Vigorous fluid administration has been successfully employed to prevent ARF in patients at high risk, including cardiac surgery, renal transplantation, hemoglobinuria, myoglobinuria, early tumor lysis syndrome, and administration of nephrotoxic agents such as radiocontrast, cisplatin, and amphotericin. Adjunctive pharmacologic agents for the prevention of ARF, including diuretics and 'renal dose' dopamine, are still widely used in the ICU setting, even though they have been shown to be ineffective and perhaps even deleterious.[28,29,60] The administration of these agents early in the course of ARF does not alter the natural history of the disease, but can potentially convert the syndrome from an oliguric to a non-oliguric form and therefore simplify fluid, electrolyte, and nutritional therapy. One common and reasonably safe clinical approach is to use high-dose furosemide (2–5 mg/kg/dose bolus followed by a continuous drip) for oliguria of less than 48 hours' duration that has not responded to adequate hydration.[73,74]

Concluding remarks

Acute renal failure represents a very significant and potentially devastating problem in pediatric medicine. The precise incidence of pediatric ARF is not known, but appears to be rising. Ischemia and nephrotoxins are the leading causes of ARF in the native as well as the transplanted kidney. Outstanding advances in basic research have illuminated the pathogenesis of ischemia-reperfussion injury (IRI) and have paved the way for successful therapeutic approaches in animal models. However, translational research efforts in humans have yielded disappointing results. A major reason for this is the lack of early markers for ARF, akin to troponins in acute myocardial disease, and hence an unacceptable delay in initiating therapy. In current clinical practice, ARF is typically diagnosed by measuring serum creatinine, which is an unreliable indicator during acute changes in kidney function. However, animal studies have shown that whereas ARF can be prevented and/or treated by several maneuvers, these measures must be instituted very early after the insult. The lack of early biomarkers of acute renal injury in humans has hitherto crippled our ability to launch potentially effective therapies in a timely manner. Indeed, several human investigations have now established that the earlier the intervention, the better the chance of ameliorating the renal dysfunction. Conversely, the longer the duration of ARF, the greater is the mortality. Fortunately, several potential candidates are currently being developed and tested as early biomarkers of acute renal injury. It is likely that not any one biomarker but a collection of strategically selected proteins may provide the hitherto elusive 'ARF Panel' for the early and rapid diagnosis of acute renal injury. Such a tool would be indispensable for the timely institution of potentially effective therapies in human ARF, a common clinical condition still associated with a dismal prognosis where early intervention is desperately needed.

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25 Hemodialysis

Jordan M Symons and Sandra L Watkins

Hemodialysis is the most efficient method of artificial renal support, accomplishing molecular transfer at much higher rates than either peritoneal dialysis or continuous renal replacement therapies. It is highly effective in acute settings for management of critical volume overload or intoxication, and serves as an important method for chronic maintenance dialysis. Children require special evaluation and monitoring for successful hemodialysis. This chapter will discuss general principles of hemodialysis operation, vascular access, prescription, and management with emphasis on the unique considerations for pediatric patients.

History of hemodialysis

Kolff used the rotating-drum artificial kidney for the first time in 1943.[1] This large, cumbersome device gradually gave way to more sophisticated modern dialysis machines that make use of integrated technology, precise electronic controls, and off-the-shelf disposable materials. Although the early therapy was successful in removing uremic toxins and improving clinical status, patients could not receive hemodialysis for more than a few sessions due to lack of permanent vascular access and rapid loss of vascular sites from repeated punctures. Scribner and Quinton developed the arteriovenous shunt in 1960, which allowed patients with chronic renal failure to receive ongoing hemodialysis.[2] Surgical techniques for creation of dialysis vascular access have also matured over the last four decades. These advances have permitted the widespread use of hemodialysis.

The complexities of hemodialysis originally made its application to small pediatric patients difficult. Technical improvements, experience, and highly skilled nursing staff now permit the use of hemodialysis in all children, even in the newborn. The dual-lumen vascular catheter, such as that developed by Hickman, makes vascular access in smaller children feasible.[3] Hemodialysis machines with precise ultrafiltration control allow accurate management of intravascular volume in small patients, in whom significant morbidity can result from minor shifts in intravascular volume. Protocols and guidelines, based on evidence and expert opinion, continue to improve the quality of hemodialysis for pediatric patients.[4,5]

Epidemiology of pediatric hemodialysis

The United States Renal Data System (USRDS) tracks statistical information for patients in the United States with end-stage renal disease (ESRD). The USRDS Annual Data Report indicates that 2347 patients under 20 years old were on chronic dialysis at the end of the year 2002. Of these, 1353 (57.6%) received hemodialysis as their dialysis modality.[6]

Older children are more likely to use hemodialysis as the modality of treatment for ESRD. Twenty two percent of children with ESRD on dialysis from the newborn period up through age 4 years receive maintenance hemodialysis, as compared with 40% of children on dialysis from ages 5 to 9 years, 50% of children ages 10 through 14 years, and 71% of children from ages 15 through 19 years.[6] By contrast, the USRDS data reveal that hemodialysis is the modality of choice for 91% of prevalent ESRD dialysis patients 20 years of age or older (Figure 25.1). There has been growing use of hemodialysis as the initial dialytic modality for children. USRDS data report 63% of incident pediatric ESRD patients beginning maintenance dialysis in 2002 started with hemodialysis.[6]

Hemodialysis can be used successfully for management of acute renal failure. Because of its efficiency, hemodialysis is also

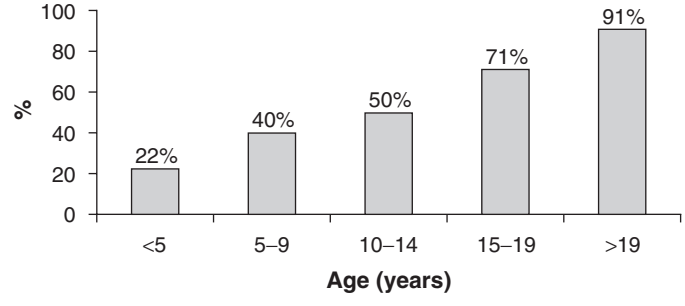

Figure 25.1 Percentages of prevalent end-stage renal disease patients receiving hemodialysis as their dialysis modality, separated by age groups. (Data from USRDS Annual Data Report.[6])

an excellent choice in the acute setting for the treatment of other clinical conditions, such as intoxications, volume overload, inborn errors of metabolism, and hyperkalemia.

Principles of hemodialysis

The following basic physical principles of solute transport underlie all modalities of renal replacement therapy, including hemodialysis (Figure 25.2):

- **Diffusion**: is the process whereby molecules pass from an area of higher concentration to an area of lower concentration across a semipermeable membrane. Due to energy considerations, smaller molecules diffuse across a membrane more rapidly than larger molecules.
- **Convection**: is the hydrostatic pressure-related movement of other molecules, dissolved in water, across a semipermeable membrane. Due to the hydrostatic pressure, small and large molecules tend to be removed equally, up to the molecular size cut-off point of the semipermeable membrane. Molecules larger than the membrane pores are not able to pass.
- **Ultrafiltration**: is the movement of water across a semipermeable membrane due to the force of hydrostatic pressure.

Hemodialysis combines all three of the above principles of solute and water transport. The patient's blood passes through a dialyzer, which serves as a semipermeable membrane. Dialysate flows through the dialyzer on the outer side of the semipermeable membrane, and serves as a medium into which molecules from the blood can diffuse. The application of hydrostatic pressure to the dialyzer membrane leads to ultrafiltration of water from the blood, as well as convective removal of molecules, up to the limit of the dialysis membrane pores size. Through manipulation of the components of the dialysis prescription, one can control the level of diffusion, ultrafiltration, and convection to achieve specific goals for a given patient.

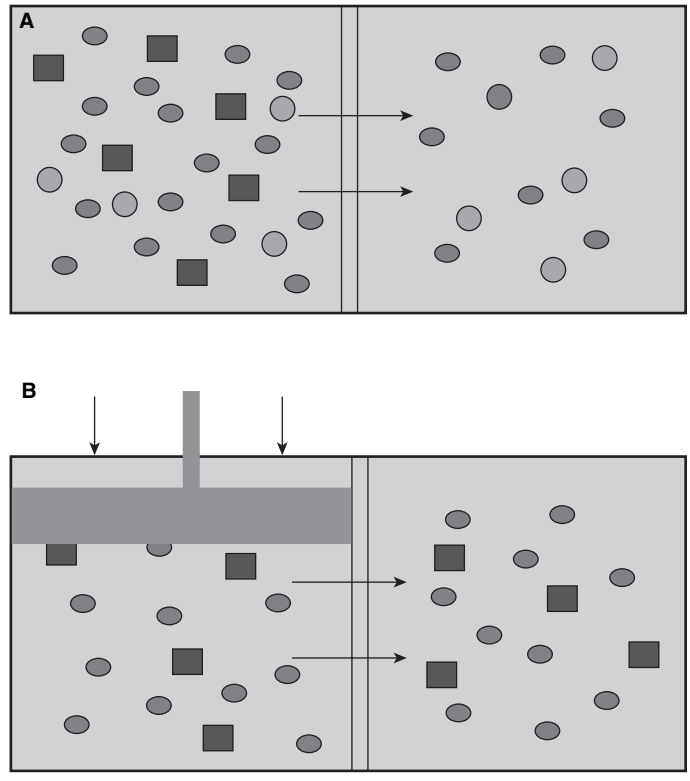

Figure 25.2 (A) Diffusion. Smaller molecules pass from higher concentration to lower concentration across a semipermeable membrane. Larger molecules are restricted. (B) Convection. Small and larger molecules pass across a semipermeable membrane under the effects of pressure. (Reproduced with permission from Pediatric Critical Care, 3rd edn, Fuhrman and Zimmerman (eds). © 2005 Mosby and Company Publishers with permission by Elsevier.

Dialysis equipment

Dialyzers

Early dialysis membranes have given way to modified cellulosic membranes and to those made from synthetic materials. These synthetic membranes are considered more biocompatible and are less likely to cause adverse reactions. Dialyzer design has also changed dramatically since the earliest methods of hemodialysis. Dialyzers of the hollow-fiber design have replaced old-style Kiil flat plate dialyzers, which required assembly for individual patients and careful maintenance.

Hollow-fiber dialyzers consist of a tube-shaped plastic cartridge through which pass numerous hollow capillary fibers made of semipermeable dialysis membrane material. This yields a large surface area for diffusion, ultrafiltration, and convection. Blood enters the dialyzer at one end and distributes through the hollow-fiber capillaries. The hollow fibers coalesce and are 'potted' at the two ends of the dialyzer, which serve as the ports for entry and exit of the patient's blood. The dialysate ports are present on the side of the dialyzer tube. Dialysate enters the dialyzer cartridge through the dialysate port, flows between the numerous hollow-fiber capillaries in a direction countercurrent to the flow of blood. Thus, the lumen of the capillary fibers represents the 'blood side' of the semipermeable membrane and the space outside of the fibers serves as the 'dialysate side'.

Hollow-fiber dialyzers are mass-produced by many manufacturers worldwide and come in a variety of sizes, surface areas, and characteristics. There are, however, few dialyzers currently available of an appropriate size for hemodialysis of the smallest pediatric patients.

Dialysate

Early hemodialysis machines required preparation of dialysate in large batches in order to meet patient needs. Present-day dialysis machines allow preparation of dialysate on-line from concentrates mixed with purified water. Changing the base concentrates or the admixture yields adjustment to the final

dialysate electrolyte composition. Such an arrangement allows the staff to vary dialysate prescription, based on individual patient requirements.

Water quality

The blood of a hemodialysis patient is exposed to a large volume of dialysate during a hemodialysis session. Using a standard dialysate flow rate of 500 ml/min, a patient receiving hemodialysis for 3 hours each session, three times a week, will encounter 270 L of fluid on a weekly basis. Consequently, the water used to generate dialysate must meet rigorous standards for chemical, bacteriologic, and endotoxin content. Municipal water is purified by employing carbon filtration and reverse osmosis (RO). Depending on the chemical composition and hardness of the municipal water, it may be necessary to employ a water softener before it is subjected to RO. Guidelines for water purity for dialysis use are updated periodically and published in the United States.[7]

Dialysis machine

The hemodialysis machine is composed of several interacting components (Figure 25.3).

Blood pump

The blood pump is a central mechanical component of the dialysis machine that pumps the blood out of the patient into the blood tubing; this column of blood then traverses the 'blood loop' through the dialysis machine. Pressure transducers within the blood loop monitor the pressure of the blood column as it passes through the blood tubing to and from the patient, and through the dialyzer.

Dialysate proportioning system

The dialysate proportioning system mixes dialysate concentrates with purified water, tests the final dialysate for conductivity (as a measure of electrolyte content), and delivers the dialysate into the dialyzer through a separate dialysate loop.

Ultrafiltration controller

Early dialysis machines required careful calculation of transmembrane pressures necessary to achieve required ultrafiltration. Modern dialysis machines employ computerized ultrafiltration control devices that automatically control transmembrane pressure to deliver the prescribed rate of ultrafiltration.

Safety devices

Numerous safety mechanisms are present in modern dialysis machines that test for appropriate pressure, temperature, and dialysate content. Test failure causes an audible and visual alarm on the machine and may divert dialysate away from the patient or halt the dialysis machine completely. These systems are designed to ensure patient safety.

Anticoagulation in hemodialysis

The hemodialysis circuit requires anticoagulation for successful extracorporeal flow. Heparin is the most commonly used anticoagulant for the dialysis procedure. Patients usually receive an initial bolus of heparin (20–40 units/kg) into the blood loop of

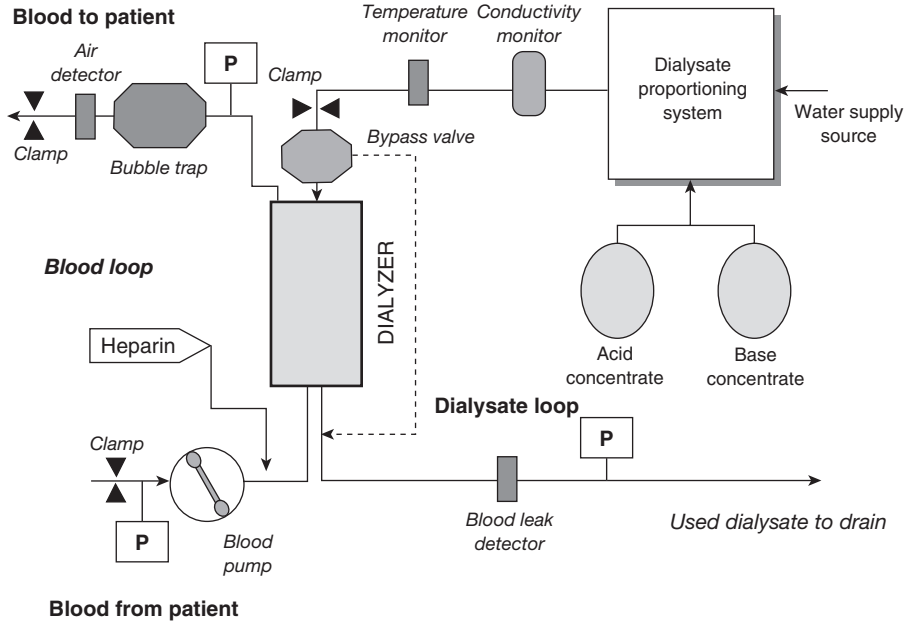

Figure 25.3 Schematic representation of hemodialysis circuit blood loop and dialysate loop. Boxes marked 'P' represent pressure monitors.

the hemodialysis circuit at the start of dialysis. A continuous infusion at lower dose (10–20 units/kg/h), or periodic boluses of heparin, can be employed in order to achieve therapeutic anticoagulation.

Heparin use requires careful monitoring and clinical judgment in order to maintain circuit anticoagulation, while minimizing heparin exposure and risk of bleeding in the patient. The clinician may monitor the activated partial thromboplastin time (aPTT) or activated clotting time (ACT) to determine appropriate heparin dosage. The target ACT for hemodialysis should be 1.25–1.5 times baseline, usually 180–220 seconds, using the Hemochron device, and aPTT should be between 120 and 160 seconds.[8,9] Low molecular weight heparin, hirudin, and citrate have also been used as anticoagulants for the hemodialysis procedure.

Hemodialysis can also be performed successfully without anticoagulation, especially if the risk of bleeding is high. In this situation, intermittent flushing of the dialyzer with saline (20–30 ml) can maintain circuit patency. While avoiding heparin exposure, clotting of the extracorporeal circuit, with subsequent loss of extracorporeal blood volume, remains a risk with this technique.

Vascular access

Hemodialysis requires an adequate vascular access that permits sufficient blood flow through the dialysis system. Vascular accesses used in clinical practice include indwelling catheters, surgically created native arteriovenous fistulae (AVFs), and artificial subcutaneous arteriovenous grafts (AVGs). Placement of vascular access in children, especially in infants, is often difficult, due to the small size of blood vessels in children, and requires considerable skill on the part of the surgeon or an interventional radiologist.

Vascular access for acute hemodialysis

Acute vascular access for hemodialysis is most often accomplished by placement of a double-lumen dialysis catheter in the internal jugular or femoral vein. These sites usually provide adequate blood flow and are acceptable for short-term use in the hospitalized patient. The subclavian vein catheter insertion should be avoided because of the risk of venous stenosis (see below).

Acute double-lumen dialysis catheters lack a subcutaneous cuff, and are designed for insertion at the bedside, using the Seldinger technique. These catheters come in a variety of sizes, including 7 French catheters that are suitable for use in infants. Should even the smallest catheter prove too large for an infant requiring vascular access, two single-lumen 5 French catheters can be inserted at two separate venous sites (Table 25.1).

Table 25.1 Acute dialysis catheter choices

Patient size	Catheter choice
Neonate	7 French double-lumen 5 French single-lumen (requires two separate catheters)
3–6 kg	7 French double-lumen
6–30 kg	8 French double-lumen
15–30 kg	9 French double-lumen
>30 kg	10 French double-lumen 12.5 French double-lumen

Long-term central venous dialysis catheters

For patients who require longer-term vascular access for hemodialysis, a catheter can be placed in the internal jugular position with the access ports tunneled under the skin to exit on the chest. This redirected exit site is more comfortable for the patient and cosmetically more appealing as the catheter exit can be hidden under clothing. A Dacron cuff on the catheter resides within the subcutaneous tunnel. This aids in fixing the catheter in place and limits migration of bacteria along the subcutaneous track. Because of the concerns of venous stenosis, subclavian vein catheter placement for vascular access should be avoided.

There are few long-term hemodialysis catheters available for children. The smallest commonly available double-lumen catheter is 8 French; even if the diameter is acceptable, the catheter may be too long for ideal positioning in a small pediatric patient. Highly effective catheters with novel designs that separate the paired internal lumens can provide improved flow dynamics and have been used successfully in adults. Such systems may be appropriate for the older child or adolescent[10] but are not available in sizes acceptable for young children.

Care of dialysis catheter

The hemodialysis catheter requires special care. As with any central venous catheter, the exit site must be kept clean and dry. Appropriate dressing is applied to the exit site. In the outpatient setting, patients and families must be taught to care for the catheter between dialysis sessions. To limit the chances of thrombosis, high doses of heparin are usually instilled into the catheter. The concentration of heparin is often between 1000 units/ml and 5000 units/ml. Heparin instilled in the catheter must be carefully removed from the catheter at the time of the next dialysis session and catheter access. To prevent accidental infusion of this anticoagulant, and to preserve sterility and adequate function, many dialysis programs strictly proscribe access to the hemodialysis catheter, reserving this important task for only trained dialysis personnel.

While hemodialysis catheters can be used immediately after placement and can be accessed with no discomfort to the patient, they suffer from a relatively high rate of failure and complications. Hemodialysis catheters are prone to infection

and thrombosis formation, which can lead to patient morbidity and may necessitate catheter revision or complete removal.[11–13] Flow dynamics through a hemodialysis catheter may be suboptimal, requiring extended dialysis time to accomplish similar levels of mass transfer. Use of thrombolytic agents such as tissue plasminogen activator (tPA) may be necessary to improve flow characteristics in a hemodialysis catheter with thrombosis.

Permanent vascular access

For any patient with chronic renal failure in need for long-term maintenance hemodialysis, careful consideration should be given to the creation of a permanent subcutaneous vascular access. In patients with slowly progressing renal failure, a permanent vascular access can be created before the patient requires hemodialysis, thus avoiding the use of a dialysis catheter. The clinician, patient, and family should begin discussions about vascular access early in the medical relationship.

The native AVF remains the gold standard for hemodialysis vascular access. Fully contained under the skin and created from native blood vessels in situ, a hemodialysis fistula can provide safe vascular access for decades with the lowest rates of complication. Successful creation of a hemodialysis fistula requires an acceptable arterial and venous anatomy, in addition to an experienced surgeon. The fistula is often attempted at the distal forearm of the non-dominant hand. The cephalic vein is connected to the radial artery, causing preferential blood flow at high velocity through the newly created anastomosis. The vein expands and its walls thicken as the fistula matures. Adequate flow in the fistula may take 6–8 weeks to evolve, but it may take up to 4 months for the walls of the fistula to thicken and become strong enough to withstand intermittent puncture with needles for hemodialysis access. Some fistulae never mature (primary failure). In such cases, alternative sites or methods of vascular access need to be considered.

As an alternative to the native AVF, the surgeon may consider placement of a subcutaneous AVG. Most commonly used AVGs are made of polytetrafluoroethylene (PTFE). This artificial conduit between an artery and vein provides vascular access without the need for extended time for maturation. A PTFE graft is often ready for cannulation shortly after placement, once the graft has been well incorporated. Grafts made of newer materials can be cannulated almost immediately. Grafts can be placed in the forearm, upper arm, and in the thigh. Primary failure is less common with a PTFE graft as compared to a native fistula, but long-term survival of PTFE grafts is lower; a frequent problem is the development of stenosis at and around the venous anastomosis.

Monitoring of permanent vascular access

A permanent hemodialysis vascular access requires monitoring over the long term. Development of collateral blood vessels in an AVF, or stenosis in the fistula or a PTFE graft can limit blood flow through the vascular access and diminish the effectiveness of the hemodialysis procedure. Continued reduction of flow can lead to sludging and thrombosis in the access itself; such a situation requires immediate attention to prevent permanent failure of the access. The clinician should examine the access regularly and review its function with dialysis staff. Rising dynamic pressure over several hemodialysis sessions may suggest diminished flow or stenosis in the vascular access; however, several factors, including patient position, needle placement, and clinical status, may have an impact on observed dynamic pressure. For this reason, evaluation of access flow by the ultrasound dilution technique has gained favor to monitor for changes in flow that might presage diminished function and failure.[14,15]

A computer-linked device used in the dialysis unit during a hemodialysis session measures the changes that occur in the velocity of an ultrasound signal when a bolus of saline is introduced into the vascular access. Regular evaluation of the vascular access with this device permits monitoring of the change in access flow. Patients with a noted decline in access flow on routine measurement may be referred for more complete imaging evaluation by Doppler ultrasound or by angiography. This method allows for early intervention and may prolong the life of the vascular access.

Treatment of venous stenosis

Stenosis of the permanent vascular access is a common cause of poor access function and can lead to thrombosis and loss of the vascular access. When screening methods or imaging studies reveal a venous stenosis, percutaneous transluminal angioplasty can be an effective therapy. Surgical intervention may be necessary. A pediatric dialysis service must develop a close working relationship with vascular surgeons and interventional radiologists trained in these techniques.

Preserving potential vascular access sites

Children with chronic renal failure face a lifetime need for vascular access; even those who undergo successful renal transplantation may experience allograft failure and may need to return to dialysis. Consequently, preservation of potential vascular access sites is of paramount importance. Patients with chronic renal failure should avoid phlebotomy or intravenous catheter placement in the non-dominant arm, especially in the cephalic vein where a permanent dialysis access may need to be created in the future. Radial artery puncture should similarly be avoided. For patients who require a central venous catheter, clinicians should refrain from placing the catheter in the subclavian position, so as to limit the likelihood of future subclavian vein stenosis and venous outflow obstruction.[16,17] Such obstruction, even when mild, can greatly hamper successful creation of a permanent dialysis access in the ipsilateral arm.

Patient selection for hemodialysis

Choice of dialysis modality in the acute setting is often dictated by the clinical indications. Hemodialysis may be preferred when rapid correction of metabolic abnormalities is needed,

or when a medical condition precludes the use of peritoneal dialysis. For chronic maintenance dialysis, patient and family preference should be considered along with medical needs. Whereas the majority of maintenance hemodialysis patients receive their therapy at a hemodialysis center, some programs offer home hemodialysis as an option.

Hemodialysis prescription

Hemodialysis prescriptions for pediatric patients need to be individualized. The clinician must consider the size of the patient, the clinical status, and the therapeutic goals of the dialysis session. From this starting point, one may choose an appropriate dialyzer, tubing set, blood pump speed, dialysate mixture, anticoagulation plan, ultrafiltration goal, and duration of therapy (Table 25.2).

Blood flow rate

Blood flow rate is determined by vascular access. Large-size double-lumen hemodialysis catheters (>12 French size) will be able to provide a blood flow rate of at least 200 ml/min. By contrast, smaller-caliber catheters (e.g. 8 French size) may only be able to produce a blood flow rate of 75–100 ml/min. Permanent vascular access (fistulae and grafts) provides vastly superior blood flow rates of 300 ml/min, or higher. Higher blood flow improves the efficiency of the hemodialysis session and permits greater mass transfer in a given period of time.

Dialysate flow rate

The standard dialysate flow rate is 500 ml/min. Some dialysis machines permit wider variation of the dialysate flow rate, allowing flows as high as 800 ml/min. This also increases dialysis efficiency but has lesser impact than changes in blood flow rate.

Extracorporeal blood volume consideration

Traditional physiologic principles suggest that the total extracorporeal volume of the blood circuit (tubing and dialyzer) should not exceed 10% of the patient's blood volume. Pediatric tubing sets and dialyzers with small priming volumes have been developed for smaller patients. Even the smallest external volume may exceed these limits when performing hemodialysis on infants. In this setting, priming of the circuit with blood or colloid may be necessary to prevent hypotension at dialysis initiation.

Table 25.2 Components of the hemodialysis order

Frequency of dialysis
Individual session length
Type of vascular access to be used:
- Catheter
- Fistula or graft:
  - Needles for fistula or graft

Dialyzer
Tubing set
Tubing system prime:
- Blood
- Albumin
- Saline
- Self

Blood flow rate
Dialysate flow rate
Dialysate components:
- Sodium program (concentration, modeling)
- Bicarbonate concentration
- Potassium concentration
- Calcium concentration
- Special dialysate formula or components

Anticoagulation:
- Initial heparin dose
- Continuous heparin infusion
- Intermittent heparin dose

Ultrafiltration plan:
- Ultrafiltration goal or target weight
- Ultrafiltration modeling or profile

Monitoring:
- Activated clotting times (frequency/goals)
- Blood pressure monitoring (frequency/goals)
- Special monitoring (as indicated):
  - Cardiac monitor
  - Pulse oximetry
  - One-to-one nursing

Dialysis-associated medications (as indicated):
- Erythropoietin
- Iron
- Vitamin D analogue
- Antibiotics
- Special medications

Laboratory tests (as indicated):
- Blood chemistries (e.g. pre- and post-BUN)
- Complete blood count
- Blood cultures
- Special blood tests

Access care and monitoring:
- Catheters:
  - Dressing change plan
  - Indwelling heparin following dialysis
- Fistulae and grafts:
  - Pressure/flow monitoring plan

Dialyzer selection

The clinician selects the dialyzer with consideration to the biocompatibility of the membrane, priming volume, clearance, and ultrafiltration characteristics. A dialyzer with a larger surface area and greater permeability permit greater mass transfer and ultrafiltration, but the volume of blood required to fill such a dialyzer may be too large for a small child. Slow blood flow, as might be seen with a small-caliber catheter in a pediatric patient, will reduce the efficiency of mass transfer even in a larger dialyzer and may increase the likelihood of clotting. Consequently, the choice of dialyzer depends on a balance of multiple factors.

The permeability surface area product, or mass transfer area coefficient (KoA), describes the mass transfer potential of any given dialyzer. KoA, measured in milliliters per minute, is an intrinsic property of the dialyzer, and is a function of the permeability to the solute in question (Ko) and the dialyzer surface area (A). Dialyzers with higher KoA will tend to have a greater ability to transfer solute during the dialysis session. Clearance (K_D), which describes the function of a given dialyzer in a particular clinical situation, is based not only on the KoA, but also on the blood flow rate (Q_B) and the dialysate flow rate (Q_D). K_D is lower with lower blood and dialysate flows, and increases, within limits, with higher flows. Consequently, the actual clearance achieved by a given dialyzer depends on operational characteristics beyond the KoA of the dialyzer.

The ultrafiltration coefficient (K_{UF}) similarly describes the ability of the dialyzer to move water across the membrane at a given transmembrane pressure. Dialyzer manufacturers publish values for KoA and K_D for urea (the molecule used most often for dialysis prescription) and K_{UF}, providing the clinician with tools that permit comparison and selection of an appropriate dialyzer for an individual patient.

Time on dialysis

Greater time on dialysis permits greater mass transfer of both small and middle molecules. In addition, longer time may allow more successful ultrafiltration, as the rate of fluid removal can be lowered, reducing the likelihood of symptoms related to rapid emptying of the vascular compartment. Extended time on dialysis for the chronic patient, requiring travel to the dialysis unit, lost time in school, and fewer opportunities for play, may have a negative impact on quality of life.

Determinants of prescription

Use of the mass transfer equation can guide the clinician's choice of dialyzer, blood pump speed, and session length. The mass transfer equation describes the changing concentration of a given molecule within the patient based on the dialysis session parameters (Figure 25.4):

$$C_t/C_0 = e^{-Kt/V}$$

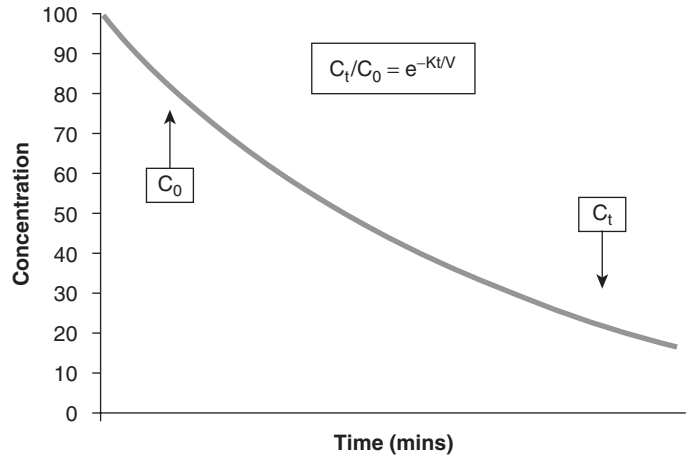

Figure 25.4 The mass transfer equation describes the concentration of a molecule within the patient during the dialysis session. C_0 = concentration of molecule at time zero; C_t = concentration of molecule at time t; K = dialyzer clearance coefficient for molecule in question; t = time in minutes; and V = volume of distribution of molecule in question, in milliliters.

where C_t and C_0 are the concentrations of the molecule in question at time t and at session start (time zero), respectively; K is the clearance coefficient for the molecule in question; t is session length in minutes; and V is volume of distribution for the given molecule, in milliliters. Blood urea nitrogen (BUN) is the most commonly used molecular marker for determining the dialysis prescription. The above formula is particularly useful in gauging dialysis prescription in the circumstances of acute hemodialysis, or with initiation of chronic hemodialysis.

Example

Consider a new patient weighing 40 kg with a starting BUN concentration of 100 mg/dl. The clinician anticipates a blood pump speed of 200 ml/min, and selects a dialyzer that has a mass transfer coefficient of 180 ml/min (K_D for urea) at the given blood pump speed, based on the manufacturer's published data. Urea distributes within the total body water, which can be estimated as 60% of the body weight, or 24 000 ml in this case. Initial hemodialysis sessions often target lower levels of mass transfer to prevent the complications of dialysis dysequilibrium (see below). A 30% reduction of urea to a final target value of 70 mg/dl is reasonable in this case. To determine the length of the hemodialysis session with these parameters, the mass transfer equation can be rearranged to solve for t:

$$t\ (\text{minutes}) = -\ln (C_t/C_0) \times (V/K)$$

$$t\ (\text{minutes}) = -\ln (70/100) \times (24\,000/180)$$

$$t\ (\text{minutes}) = -\ln (0.7) \times 133.3 \quad \text{(natural log determination from scientific calculator)}$$

$$t\ (\text{minutes}) = -(-0.357) \times 133.3$$

$$t\ (\text{minutes}) = 0.357 \times 133.3$$

$$t\ (\text{minutes}) = 48$$

The mass transfer equation provides the clinician with a useful tool to manipulate the hemodialysis prescription. One can adjust the value of K by choosing an appropriate dialyzer, or changing blood pump speed. This, along with adjusting the dialysis session time, can provide the desired level of mass transfer necessary for the given clinical situation. Measurement of BUN levels immediately before and after the dialysis session permits evaluation of the predicted mass transfer and subsequent fine-tuning of the prescription.

As previously noted, the clinician often chooses an initial hemodialysis prescription for new, highly uremic patients that provides for urea reduction of no greater than 25–30%. The patient undergoes hemodialysis for three or four consecutive days, each day with progressively higher levels of mass transfer, until a 'full dose' of >70% urea reduction is achieved.

Ongoing dialysis prescription and schedule depends on the clinical situation. In the acute setting, only one or two hemodialysis sessions may be required for the treatment of intoxication, whereas other patients with acute renal failure may be served best by daily hemodialysis to limit metabolic fluctuation, maintain relative volume stability, and permit delivery of fluids, medications, and nutrition. Other patients with more persistent acute renal failure, or those with chronic renal failure who require maintenance dialysis, may receive hemodialysis on an alternate-day or three times a week schedule. Individual clinical needs may necessitate hemodialysis more frequently.

In addition to determining metabolic goals, the clinician must also choose a plan for ultrafiltration during the hemodialysis session. Ultrafiltration control devices on modern hemodialysis machines permit precise levels of fluid removal throughout the hemodialysis session. The clinician must make a judgment as to the level of ultrafiltration that the patient can tolerate in the given session time. The hemodialysis machine can then be programmed to remove fluid from the patient at the desired rate. Careful monitoring of blood pressure, heart rate, and general patient status is required as the intravascular compartment volume contracts. This is especially true with smaller pediatric patients in whom minor fluctuations in intravascular volume can have significant hemodynamic consequences. New blood volume monitoring devices (Critline), which non-invasively measure the change in the patient's hematocrit during dialysis, can also be useful in monitoring fluid removal during dialysis.[18,19]

Hemodialysis dose and adequacy

Urea kinetic modeling (Kt/V)

Determining the optimal dose of maintenance hemodialysis remains difficult. Using data from the National Cooperative Dialysis Study (NCDS), Gotch and Sargent developed a method using the removal of urea as a proxy for the dose of hemodialysis.[20] Higher levels of urea removal are equated with a higher dialysis dose. Despite controversy, this method of using urea as an acceptable marker for small molecule clearance remains a standard method for measuring the quantity of dialysis delivered to the patient.[5]

The urea kinetic model requires simultaneous solution of complex differential equations, necessitating the use of computational software. Simplified logarithmic formulae, such as that described by Daugirdas,[21] approximate the results of formal urea kinetic modeling. Data necessary for both the formal model and the logarithmic approximation include patient BUN levels just before and just after a dialysis session, patient weight, time of the dialysis session, and amount of fluid removed by ultrafiltration.

The formal urea kinetic model as well as the logarithmic formula lead to the calculation of a mathematical derivative, known as 'Kt/V'. This dimensionless number is familiar as a component of the mass transfer equation. One may evaluate Kt/V and the movement of urea using a single-pool model or a more complex double-pool model, which takes into account urea kinetics between cells and the vascular compartment. Based on the early evaluation of the NCDS data and subsequent study, minimum levels of Kt/V have been established for adult populations.[5] Newer data, however, have called into question the primacy of urea kinetics. In one such study, there was no improvement in survival of adult patients receiving higher dose of dialysis (higher Kt/V).[22]

Urea reduction ratio

Urea reduction ratio (URR) is a much less complex technique that can be used as a measured delivered dialysis dose. The calculation of URR is based on the simple ratio of the pre- and postdialysis BUN levels:

$$\text{URR} = \frac{\text{Postdialysis BUN}}{\text{Predialysis BUN}} \times 100$$

It is important to note that URR is not capable of considering multicompartment issues, as is done in urea kinetics formulas. In addition, formal urea kinetics can provide important data relating to patient's nutrition through analysis of a secondary result known as the normalized protein catabolic rate (nPCR), or normalized protein equivalent of nitrogen appearance (nPNA). Assuming no excessive protein consumption or loss, the nPCR (nPNA) represents the patient's level of protein intake. This parameter can assist in evaluating nutritional status while on maintenance hemodialysis.[23]

Current recommendations suggest that for patients on chronic maintenance hemodialysis for three sessions per week, the delivered single-pool, variable volume Kt/V should be at least 1.2 and the average URR should be at least 65%.[5] Outcome data support these guidelines for adults. As there are no data linking delivered dose of dialysis and outcome for pediatric patients, the recommendations for children are based on opinion.

Technique of sampling

The accuracy of Kt/V and URR measurements depends on appropriate sample collection. Dialysis staff must obtain blood

samples for BUN before and after the dialysis session using a standardized technique. The predialysis BUN sample must be obtained using a method that will avoid dilution of the blood and lead to a spuriously low BUN value. The recommended method for obtaining the postdialysis sample is the so-called 'slow flow/stop pump' technique. Dialysate flow is minimized, ultrafiltration is discontinued, and blood flow is reduced to 50–100 ml/min in the vascular access for 15 seconds. The blood sample is obtained from the arterial limb, either with continued slow flow through the system or after fully stopping the blood pump.[5] This approach minimizes the effect of recirculation and urea rebound, which can lead to spurious results.

Measures of dialysis dose need to be correlated with outcome. Unfortunately, the data on dose and outcome in pediatric hemodialysis are sparse. Current pediatric recommendations are based largely on expert opinion and are extrapolated from adult studies. As noted above, currently a minimum Kt/V of 1.2 is recommended.[5] Most agree, for both pediatric and adult patients, that there is a minimum threshold for dialysis dose below which a poor outcome is more likely; however, the level of dialysis that is 'optimal' remains unclear. Growing clinical data in small numbers of patients suggest that more frequent hemodialysis with schedules employing short daily sessions or long nocturnal sessions leads to improved biochemical parameters and a greater sense of patient well-being.[24,25] It seems likely that a multi-pronged approach, considering urea kinetics, phosphate clearance, blood pressure control, nutritional status, overall patient health, and other parameters, will be necessary to define the optimal level of hemodialysis.

Inadequate dialysis

Numerous factors can limit dialysis adequacy, leading to insufficient mass transfer, volume overload, and symptomatology. The clinician must evaluate the patient, laboratory values, and dialysis adequacy studies (Kt/V and/or URR) to determine whether dialysis is adequate or not. The finding of inadequate dialysis warrants an investigation into its possible causes.

Underprescription

Underdialysis may occur if the prescribed dose of dialysis is insufficient. The clinician should review all aspects of the prescription and ensure that they are optimized. This includes using the largest possible dialyzer, highest blood flow rate permitted by the vascular access, and sufficient time on dialysis. As previously noted, many of these parameters are limited in the pediatric population due to the size of the patient and technical constraints of the vascular access. Careful attention to the prescription, optimized for the individual patient, will help to avoid underdialysis.

Once prescription is optimized, delivered dose must be evaluated on a regular basis. When delivered dose falls below target levels (e.g. Kt/V < 1.2), a systematic evaluation of the technical aspects of the dialysis procedure needs be undertaken to determine if there is an identifiable cause for inadequate dialysis delivery. Published guidelines[5] describe a sophisticated algorithm for hemodialysis dose troubleshooting. Conceptually, the investigation should center on the components of the prescription under the clinician's control: namely, the clearance (K) and the effective time on dialysis (t). Other factors that may have an effect on delivered dose include blood recirculation in the vascular access and errors in obtaining the blood sample for adequacy study.

Diminished clearance

Since clearance on hemodialysis is a function of the dialyzer permeability, surface area product (KoA), blood flow rate (Q_B), and dialysate flow rate (Q_D), the clinician should consider various factors that will cause KoA, Q_B, or Q_D to differ from the values originally prescribed. Incorrect dialyzer, dialyzer volume loss due to reuse procedure, inappropriate dialysis machine settings, excessive dialyzer clotting, and machine miscalibration or malfunction are potential causes for clearance that is less than expected.

Perhaps, the most common fundamental issue leading to diminished clearance in pediatric hemodialysis is lower-than-expected Q_B, which is often a result of problems with the vascular access. Many pediatric patients are dialyzed with a central venous catheter as the vascular access which can be particularly prone to problems with blood flow due to smaller caliber, thrombosis, kinking, and malposition. AVFs created in pediatric patients take longer to mature and may not achieve the high blood flow rates seen in adults. Poorly positioned needles or stenosis in the fistula or in an AVG can cause suboptimal blood flow and inadequate dialysis. Elevated pressures in the dialysis blood circuit causing machine alarms or clinical events such as hypotension may force the dialysis staff to reduce blood flow rate. Careful assessment of the vascular access and other factors with an effect on Q_B is required when the hemodialysis delivered dose is inadequate.

Diminished effective dialysis time

The patient's time on dialysis may be shortened due to patient-related issues such as late arrival for the session or request for early termination. Misinterpretation of orders or incorrect programming of the dialysis machine can also lead to a shortened session that delivers less dialysis than intended. Clinical events such as hypotension, nausea, or cramps may cause staff to terminate a dialysis session early. Technical problems with the machine or vascular access may cause temporary cessation of the dialysis session, which, if not compensated for by extending the session, will lead to reduced effective dialysis time. The clinician must perform a review of session parameters and engage in discussion with dialysis unit staff to determine causes of diminished effective dialysis time.

Recirculation

Recirculation describes the phenomenon whereby blood that has passed through the dialysis circuit is promptly drawn back into the 'arterial end' of the blood loop upon return into the vascular access. Thus, instead of returning to systemic circulation, the dialyzed blood constantly recirculates within the dialysis circuit. This reduces dialysis efficiency and can lead to inadequate delivery of prescribed dialysis dose.

Recirculation can occur when attempting hemodialysis through a catheter using a Q_B that is too high, when needle placement in a fistula or graft is inappropriate, or when flow through the permanent vascular access is suboptimal. Low flow through a fistula or graft is of particular concern because it can presage thrombosis of the vascular access. The dialysis team can evaluate the vascular access for recirculation using an ultrasound dilution device or through blood sampling using a 'slow flow/stop pump' technique[5] that obtains blood for BUN from the arterial line, venous line, and the systemic circulation. The percent recirculation is characterized by a simple equation:

$$\text{Recirculation} = \frac{\text{Systemic BUN} - \text{Arterial BUN}}{\text{Systemic BUN} - \text{Venous BUN}} \times 100$$

A vascular access with significant recirculation (>5–10%) should be evaluated for low internal blood flow.

Errors in obtaining blood sample for adequacy study

The predialysis and postdialysis blood samples for BUN that are used in the evaluation of dialysis adequacy must be obtained using an appropriate method as described above. Inappropriate collection of the blood samples results in spurious readings that may lead to unnecessary and potentially deleterious manipulation of the dialysis prescription. The clinician should consider this possibility when dialysis adequacy studies appear to be out of range. Thorough staff education and careful adherence to appropriate protocols can minimize these errors.

Complications of hemodialysis

Complications of hemodialysis patients can be related to the hemodialysis procedure itself, the vascular access, or to renal failure itself. Complications related to renal failure are addressed elsewhere in this text.

Complications related to the hemodialysis procedure

Hemodialysis represents a fundamentally unphysiologic procedure involving extracorporeal perfusion, rapid removal of volume and small molecules from the vascular compartment, fluid shifts, changes in osmolality, and exposure of the patient's blood to foreign materials and solutions. Nevertheless, hemodialysis can be performed safely and effectively. Development of biocompatible materials, use of multiple patient safety devices, implementation of carefully designed protocols, and appropriate observation by trained staff make hemodialysis safety possible. However, complications do arise during the hemodialysis procedure, and the clinician must be aware of potential complications and of the methods to evaluate, treat, and prevent their occurrence.

Intradialytic hypotension

Low blood pressure during the hemodialysis session is a common complication, occurring in 20–50% of hemodialysis treatments, depending on the population studied and the definitions of hypotension.[26] Potential causes of intradialytic hypotension are listed in Table 25.3. A common cause in both the adult and pediatric hemodialysis centers is overly aggressive ultrafiltration that exceeds the vascular refilling rate. Hypotension can be treated by slowing the ultrafiltration rate, providing intravenous saline to the patient, and placing the patient in the head-down (Trendelenburg) position. Careful clinical evaluation and planning of ultrafiltration goals can avoid this complication. Use of a non-invasive blood volume monitor to evaluate changes in blood volume during the dialysis session has also proven successful.[18,19]

Muscle cramps

Painful muscle contractions, most often seen near the end of the dialysis session, are a frequent complication of hemodialysis therapy. These are often seen in patients who require high rates of ultrafiltration and are presumed to be related to relative intravascular volume depletion and subsequent hypoperfusion of the muscles. Electrolyte shifts during dialysis therapy are also implicated.[26] Similar to the approach with hypotension, maneuvers to permit refilling of the vascular compartment may alleviate painful cramps. Medications such as quinine have been used successfully to treat muscle cramping[27] but have not been validated in pediatric patients. Sodium modeling, the use of a dialysate sodium concentration that adjusts from high to physiologic through the dialysis session, has been reported to lessen cramps and other symptoms during hemodialysis for children and young adults.[28]

Dialysis dysequilibrium

The dialysis dysequilibrium syndrome is a neurologic disorder thought to be related to acute cerebral edema in the setting of hemodialysis. Symptoms can range from minor (headache, nausea, restlessness) to more severe findings (myoclonus, disorientation, blurred vision, seizure, coma) and even death.[26] The precise cause of the dysequilibrium syndrome is unknown; traditional teaching that it is related to development of an acute urea gradient between blood and brain in the setting of rapid hemodialysis with high BUN has not been supported by animal models.[26] Dysequilibrium is encountered less commonly now than in the past and may be related to more controlled delivery of dialysis. It has most often been seen in a first

Table 25.3 Etiology of dialysis-induced hypotension

Patient-related factors	Procedure-related factors	Uncommon causes
• Impaired plasma refilling (? decreased UF coefficient of vascular wall) • Decreased cardiac reserve (diastolic or systolic dysfunction) • Impaired venous compliance • Autonomic dysfunction (diabetic, uremic) • Arrhythmias • Anemia • Drug therapy (vasodilators, β blockers, calcium channel blockers) • Alteration of vasoactive substances in the blood • Eating during treatment (increased splanchnic blood flow) • Low dry-weight estimation	• Decreased plasma osmolality (relatively large surface area membrane, high starting BUN) • Excess absolute volume and rate of fluid removal (large interdialytic weight gain) • Change in serum electrolyte (hypocalcemia, hypokalemia) • Dialysate-acetate, too warm dialysate • Membrane–blood interaction • Hypoxia	• Pericardial tamponade • Myocardial infarction • Aortic dissection • Internal hemorrhage • Septicemia • Air embolism • Pneumothorax • Hemolysis

Adapted from Sarkar SR et al.[26]

hemodialysis session or in the setting of a very high predialysis BUN. Limiting urea reduction to approximately 30% in this setting seems to reduce the risk of dysequilibrium.

Dialysis-related allergic reactions

Exposure of blood to foreign materials during dialysis can lead to adverse reactions. Severe anaphylactoid reactions are uncommon but sterilants and components of the dialysis membrane have been implicated as potential causes.[26] These reactions often occur early in the dialysis session and may be associated with dyspnea, feeling of warmth, angioedema, urticaria, and recurrence with similar dialysis equipment.[29] The hemodialysis session should be discontinued immediately when such a reaction is suspected. Oxygen and therapy for acute allergy (e.g. antihistamines, epinephrine, steroids) may also be indicated. Future dialysis sessions should avoid the use of the offending materials. Milder reactions, usually associated with back pain and chest discomfort, can also occur. The cause is unclear and the therapy is usually symptomatic.[26] Differentiation from more severe complications such as cardiac ischemia requires careful clinical evaluation.

Air embolism

Air entry into the blood loop of the hemodialysis circuit can cause significant injury or death. This serious complication is relatively uncommon in the modern hemodialysis unit as a result of numerous patient safety devices built in the hemodialysis machines. The innovations are designed to stop the blood pump when air enters the blood loop accidentally, preventing the entry of air into the patient through the vascular access. Air potentially can enter the hemodialysis blood circuit through loose connections or cracks in the tubing system. Clinical findings depend on the amount of air that has entered the patient and the status of the patient prior to air entry. Arterial air embolism results in occlusion and distal ischemia; venous air embolism can lead to obstruction to right ventricular outflow through the pulmonary venous system. Symptoms are often non-specific and a high index of suspicion is needed to recognize this complication. When air embolism is suspected, the dialysis session is terminated with care to prevent any further air entry. The patient is placed flat and supine and provided with oxygen and volume expansion, as necessary.[30] Evacuation of the air from the vascular system requires special expertise. Careful adherence to safety procedures in the dialysis unit can prevent this potentially devastating complication.

Bleeding

Hemodialysis patients are at increased risk for bleeding due to extracorporeal perfusion of blood through the hemodialysis circuit, uremia-associated platelet dysfunction, and systemic heparinization during the hemodialysis session. A minor manifestation may be prolonged oozing from fistula or graft puncture sites; adjustment to the heparin prescription may be indicated in such circumstances. Careful titration of heparin dose and skilled nursing care can minimize the risks of more severe bleeding. Treatment for hemorrhage is supportive and includes volume expansion and correction of the acute cause. Neutralization of heparin with protamine sulfate can be considered[26] but carries risks of allergic reactions.

Complications related to vascular access

Dialysis catheters and permanent vascular access for hemodialysis (AVFs and AVGs) share a number of potential complications; other complications are unique to the type of access.

Hemodialysis catheters

Bleeding complications can occur at the time of hemodialysis catheter insertion or more rarely at a later time due to catheter erosion through a vessel. Placement of a catheter in a central vein promotes stenosis, which can complicate venous drainage from the affected limb and can limit the success of permanent vascular access placed at a later time within the drainage field of the stenotic vessel. Poor catheter function with diminished blood flow can result from catheter migration, kinking, side-hole occlusion at the catheter tip, fibrin sheath formation, or thrombosis. Repositioning of the patient, instillation of thrombolytic agents into the catheter, and surgical replacement of the catheter may be required to reestablish effective blood flow. Infection can complicate vascular catheter use; the presence of the foreign body within the patient's vascular space predisposes to bacterial infection. Aggressive use of parenteral antibiotics can salvage an infected catheter; recalcitrant infections may require catheter removal and replacement.

Permanent vascular access

Primary AVFs may fail to mature after creation. This is of particular concern in children, in whom vascular caliber is smaller than that seen in adults. Careful evaluation of the patient's vascular potential prior to surgery, coupled with an experienced surgeon, maximize the potential of successful fistula creation. AVGs avoid the issue of maturation but can be complicated by a higher failure rate. Complications of both grafts and fistulae include infection, edema of the limb, and vascular steal syndrome. These complications are seen somewhat more frequently in AVGs.[31] As noted above, permanent vascular access can also be complicated by stenosis, which may be amenable to angioplasty or surgical revision.

Outcome of hemodialysis in children

Use of hemodialysis in the acute setting has waned somewhat with the growing use of continuous renal replacement therapy (CRRT)[32] but hemodialysis remains an important modality in the acute setting, sometimes in conjunction with CRRT.[33] Outcome for children on chronic maintenance hemodialysis is somewhat more difficult to determine than for adults, since the majority of pediatric dialysis patients move on to renal transplantation. In the years 1988 to 1997, USRDS data show relatively stable 5-year survival probabilities for pediatric patients with ESRD. Five-year survival for pediatric patients who begin their ESRD therapy with hemodialysis is reported at 81%; this compares with 5-year survival of 83% for those who start with peritoneal dialysis and 92% for those who start with a transplant.[6]

Concluding remarks

Hemodialysis remains an important technique for renal replacement therapy in children. Its efficiency makes it the clear preference for selected acute indications. Well-established guidelines permit successful use in the chronic setting. Ongoing issues related to vascular access and determination of optimal dose will require continued investigation. Promising new data on maintenance hemodialysis schedules that employ more frequent sessions may point the way towards methods for improved rehabilitation of children with end-stage renal disease.

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26 Peritoneal dialysis

Bradley A Warady

Peritoneal dialysis (PD) has been recognized as an important modality for renal replacement therapy since it was first used to treat children with acute renal failure more than 50 years ago. Its relative ease of administration has also been crucial to the successful treatment of infants and young children with end-stage renal disease (ESRD). Although this chapter will not provide an exhaustive review of PD, it does address those topics felt to be most pertinent to the clinical application of this therapy and refers the reader to the extensive literature on the subject.

History of peritoneal dialysis

The peritoneal cavity has been used for the treatment of serious illness in children for at least 80 years. In 1918, Blackfan and Maxcy described the successful use of intraperitoneal injections of saline solution in dehydrated infants,[1] a method that is still used today in rural areas of some developing countries. The first reports of the use of peritoneal dialysis (PD) to treat children with renal failure were published by Bloxsum and Powell in 1948 and by Swan and Gordon in 1949.[2,3] These papers appeared when the worldwide reported clinical experience with PD was less than 100 patients.[4] As detailed by Swan and Gordon,[3] the technique allowed large volumes of dialysate to flow continuously by gravity from 20 L carboys through a rigid metal catheter that had been surgically implanted into the upper abdomen. Dialysate was constantly drained from the peritoneal cavity by water suction through an identical catheter implanted in the pelvis. Today, this technique is termed continuous peritoneal lavage, and in some ways it foretold the current emphasis on continuous as opposed to intermittent peritoneal dialysis therapies.

Swan and Gordon maintained fluid balance in their young patients by adjusting the dialysate dextrose concentration between 2 and 4 g/100 ml, as is generally done today. Excellent solute removal was achieved with an average daily dialysate delivery of 33 L. Dialysate temperature was regulated by adjusting the number of illuminated 60 W incandescent light bulbs in a box placed over the dialysate inflow path. Although two of the three children treated for acute renal failure by Swan and Gordon survived after 9 and 12 days of continuous peritoneal lavage, this technique did not attract much interest among physicians treating children with renal failure during this period, and it was more than a decade before the use of PD in children was again reported. During the 1950s, the development of disposable nylon catheters and commercially prepared dialysis solutions made PD a practical short-term treatment for acute renal failure.[5] Successful adaptation of the technique, known then and now as acute intermittent peritoneal dialysis (acute IPD), for use in infants and children with acute renal failure was first reported in 1961 by Segar et al,[6] and in 1962 by Etteldorf et al.[7]

Although successful in treating acute renal failure, PD appeared to offer little in the treatment of children with ESRD. Early acute IPD techniques required reinsertion of the dialysis catheter for each treatment,[8] making prolonged use in small patients essentially impossible. The development of a 'permanent' peritoneal catheter was first proposed by Palmer et al,[9,10] and later perfected by Tenckhoff and Schecter.[11] This made long-term IPD an accessible form of renal replacement therapy (RRT) for adult and pediatric ESRD patients. Boen et al[12] and Tenckhoff et al[13] independently devised an automated dialysate delivery system that could be used in the patient's home. With this development, long-term IPD became a practical and potentially desirable alternative to long-term hemodialysis (HD) for children with ESRD.

A new era in the history of PD as a treatment for children with ESRD was heralded by the description in 1976 by Popovich et al of a 'novel portable/wearable equilibrium dialysis technique', continuous ambulatory peritoneal dialysis (CAPD).[14] Pediatric nephrologists were quick to recognize the potential advantages CAPD offered to their young patients, perhaps because PD was familiar to those who regularly treated children with acute renal failure. Advantages over HD of special importance to children included near steady-state biochemical control, no dysequilibrium syndrome, greatly reduced dietary restrictions and fluid limits, and freedom from repeated dialysis needle punctures. CAPD also allowed children of all ages to receive dialysis in the home and thus to have more normal childhoods. Importantly, CAPD and later automated peritoneal dialysis (APD) made possible the routine treatment of very young infants with ESRD, thereby extending the option of RRT to an entire patient population previously considered too young to be suitable for chronic treatment (Figures 26.1–26.5).

CAPD was first used in a child in 1978 in Toronto.[15,16] During the past quarter century, CAPD and its many modifications (which together can be called continuous peritoneal dialysis or

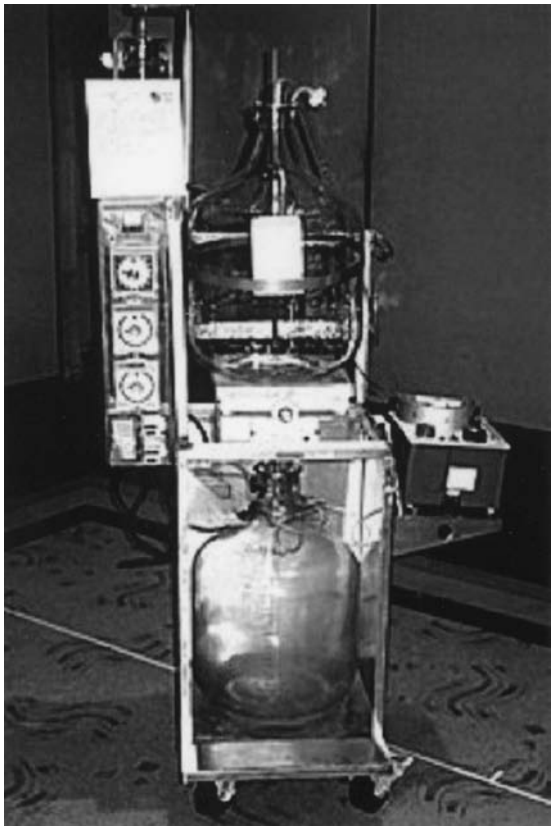

Figure 26.1 Early automatic peritoneal dialysis cycler designed by Boen et al (1960s).

Figure 26.2 Drake–Willock PD cycler machine (1970s).

CPD) have become the dialysis treatment modalities most commonly prescribed for children with ESRD throughout much of the world.[17,18]

Epidemiology of pediatric peritoneal dialysis

Dramatic growth in the use of CPD as a maintenance dialysis treatment for children occurred throughout the world during the 15 years following its introduction to pediatric dialysis.[17] By 1993, ESRD patient registry reports showed that CPD was the most commonly prescribed long-term dialysis modality for children under 15 years of age in the United States, Canada, Australia, New Zealand, the United Kingdom, the former West Germany, Israel, and the Netherlands.[19–21]

Data on CPD use in North American children have been compiled by the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). The NAPRTCS collects data on pediatric dialysis from over 152 pediatric dialysis centers located in the United States, Canada, Mexico, and Costa Rica. Between 1992 and 2003, the NAPRTCS enrolled 5392 pediatric dialysis patients (ages 1 day to 20 years).[22] Of these, the initial modality selected for 3513 (65.2%) patients was CPD, most commonly performed with an automated cycling machine. Although the majority of patients in all age groups were prescribed CPD, the preference for CPD over HD was most pronounced among younger patients: 87% of infants and young children 0–5 years of age were prescribed CPD, compared with 71% of children 6–12 years and 53% of patients >12 years of age.

It needs to be emphasized that participation in the NAPRTCS is restricted to specialized pediatric dialysis centers staffed by pediatric nephrologists, a fact that may influence observations such as dialysis modality choice. In fact, recent studies by Furth et al have shown that older children treated in non-pediatric units are more likely to receive maintenance HD than CPD.[23] To that end, information from the 2004 edition of the United States Renal Data System (USRDS) report, which addresses renal replacement therapy in the United States for all children (0–19 years) with ESRD, irrespective of their care provider (pediatric vs adult nephrologist), reveals that, at diagnosis, approximately 50% of children initiate therapy using HD, 30% with PD, and nearly 20% receive a pre-emptive kidney transplant.[18] Finally, some international data have revealed pediatric experiences elsewhere to be quite different from the United States. For example, more than 70% of

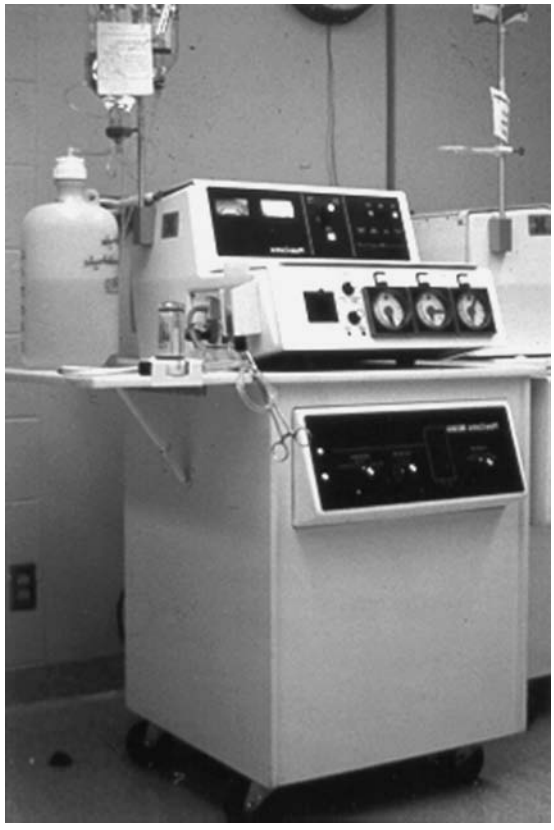

Figure 26.3 Physio–Control peritoneal dialysis cycling machine.

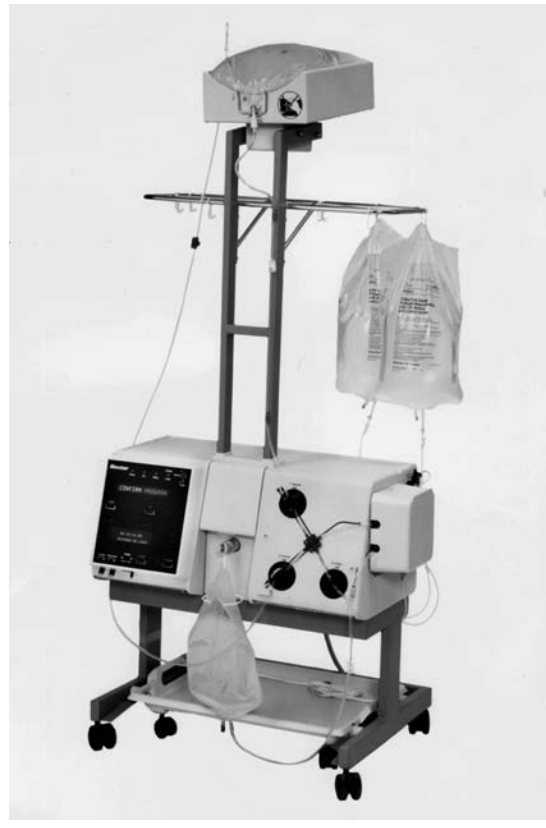

Figure 26.4 Baxter PacX automated peritoneal dialysis cycler (1984).

pediatric patients initiating dialysis in New Zealand and Scotland used CPD.[18]

Principles of peritoneal dialysis

The peritoneal exchange process is the sum of two simultaneous and interrelated transport mechanisms: diffusion and convection. Diffusion refers to the movement of solute down a concentration gradient, whereas convection refers to movement of solutes that are 'transported' in a fluid flux, the magnitude of which is determined by the ultrafiltration rate.[24]

Several theories have been developed to model the movement of water and solute across the peritoneal membrane, each progressively more complex, but each, in turn, more accurate. Recently, a comprehensive model has been developed that is known as the three-pore model. As one would expect from the name, the model postulates three types of pores:

- Ultra-small transcellular water pores or channels, which comprise perhaps 1–2% of the total pore area, yet account for 40% of water flow, and are driven by osmotic forces.
- Small pores, which are 4–6 nm in diameter and comprise 90% of total pore area. These pores are subject to both concentration gradients (diffusive forces) and osmotic gradients (convective forces).
- Large pores, which are greater than 40 nm in diameter and comprise the remaining 5–7% of total pore area. These pores allow larger molecules, such as albumin, to leave capillaries, probably driven by hydrostatic forces within the capillary bed.

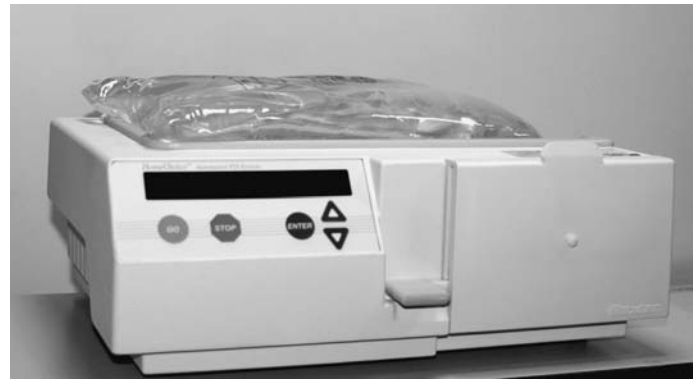

Figure 26.5 Baxter HomeChoice Pediatric peritoneal dialysis cycler (2002).

Although water moves through all three types of pores, only the small and large pores allow convective solute transfer.[25–27]

Mass transfer area coefficient

The mass transfer area coefficient (MTAC) is a value that characterizes the diffusive permeability of the peritoneal membrane and is, for the most part, independent of dialysis mechanics.[24,28] The MTAC has been variably defined as the area available for solute transport divided by the sum of resistances to peritoneal diffusion; it represents the clearance rate (expressed in ml/min) which would be obtained in the absence of ultrafiltration or solute accumulation in the dialysate.[29] The MTAC, as applied to the current three-pore model of transperitoneal solute and water flux, is equal to the product of the free-diffusion coefficient for the solute, the fractional area available for diffusion (which is a percent of the area of the unrestricted pores), and the term A_0/Δ_X, which characterizes the diffusion distance across the peritoneum.[30] To date, very few studies have measured MTACs in pediatric patients.[31–34] In the largest such study, Warady et al found evidence of enhanced transport in the youngest patients, deemed likely to be the result of differences in either permeability, effective surface area, or possibly maturational changes of the peritoneum.[34] In contrast, MTAC data have also been determined in children undergoing PD studies based on the three-pore model, with the values for children similar to those of adults when the former data are scaled to body surface area (BSA).[35]

Ultrafiltration and convection

When designing the dialysis prescription in terms of ultrafiltration, children receiving CAPD with 1.5% or 4.25% dextrose as the osmotic agent should expect the drain volume to exceed the infused volume of dialysate by 15–25% and 30–40%, respectively.[36] On the other hand, children receiving automated peritoneal dialysis with shorter dwell times (e.g. 30 minutes) with 1.5% and 4.25% dextrose dialysis solutions should expect drain volumes that exceed infused volumes by >4–8% and 12–18%, respectively.[36]

Convective mass transfer, which is dependent upon fluid removal, contributes little to the movement of small solutes, yet is responsible for most large solute removal. Studies by Pyle have demonstrated that the contribution of convection to urea transport in a 4-hour CAPD exchange with 4.25% glucose is 12%, 45% for inulin, and 86% for total protein.[37]

Early studies and much clinical experience suggested that adequate ultrafiltration could be difficult to achieve in infants and young children. Schaefer et al have suggested that the reduced ultrafiltration rate sometimes observed in infancy may actually be related to a greater total fluid 'reuptake' or reabsorption rate from the peritoneal cavity.[25] It appears that the reuptake may be secondary to either a higher lymphatic reabsorption rate (see below) or to a greater intraperitoneal pressure (IPP) in the infants that generates a reversed transcapillary flux of fluid along hydrostatic and oncotic pressure gradients.[25,38] Finally, the availability of glucose polymers (e.g. icodextrin) to serve as the osmotic agent has allowed for improved ultrafiltration in both CAPD and APD patients during long dwells, a characteristic that is essential to the maintenance of CPD in the patient experiencing loss of ultrafiltration. In a manner similar to the adult experience, de Boer et al have found that 7.5% icodextrin is capable of maintaining ultrafiltration during a 12-hour dwell in children with the ultrafiltration capacity comparable to the ultrafiltration obtained with 3.86% glucose.[39,40] Inferior results with icodextrin reported in some infants require confirmation.[41] Although a clinical definition of ultrafiltration failure has been determined in adults, comparable information is not yet available in pediatrics.[42,43]

Peritoneal fluid and lymphatic absorption

During PD, fluid is lost continuously from the peritoneal cavity, both directly into the tissues surrounding the peritoneal cavity as a result of the intraperitoneal hydraulic pressure and via lymphatic vessels.[44] Whereas lymphatic absorption is thought to account for only 20% of fluid reabsorption by some, the limited data on lymphatic absorption in children are conflicting.[45–47]

Principles of the peritoneal equilibration test

The peritoneal equilibration test (PET) was developed by Twardowski et al as a simple means of characterizing solute transport rates across the peritoneum that could have direct clinical application.[48] The construction of reference curves based on the kinetics of solute equilibration between dialysate and plasma (D:P ratio) after a 2L exchange volume, irrespective of patient size, made possible the categorization of adult patients into those with high, high-average, low-average, and low peritoneal membrane solute transport rates. PET data serve an important basis for dialysis prescription in both adults and children.

Application of a standardized PET procedure for children has resulted from an appreciation of the age-independent relationship between body surface area and peritoneal membrane surface area, and the recommended use of an exchange volume scaled to BSA whenever one conducts studies of peritoneal transport kinetics.[34,49–52] In the largest pediatric study to date, the Pediatric Peritoneal Dialysis Study Consortium (PPDSC) evaluated 95 children using a test exchange volume of 1100 ml/m^2 BSA to develop reference kinetic data (e.g. D:P and D:D_0 ratios), which can be used to categorize an individual pediatric patient's peritoneal membrane solute transport capacity (Figures 26.6 and 26.7).[34] Similar reference data have been generated from pediatric studies in Europe with a test exchange volume of 1000 ml/m^2 BSA.[52] The PET procedure in children is explained in Table 26.1.

Because the transport capacity of a patient's peritoneal membrane is such an important factor to consider when determining

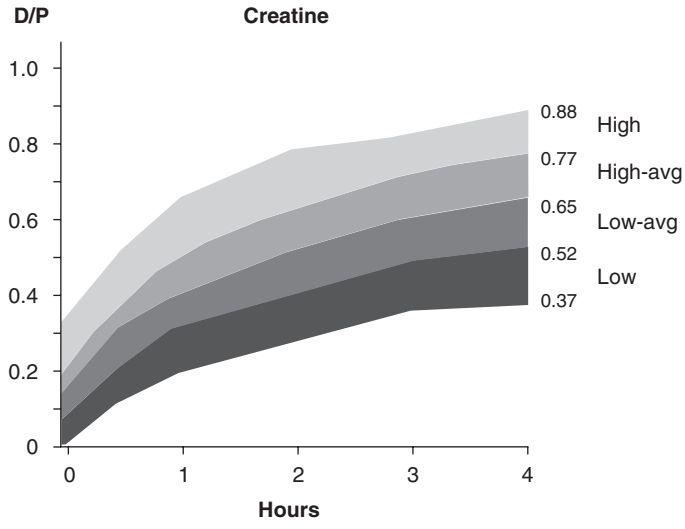

Figure 26.6 Peritoneal equilibration test results for creatinine. Shaded areas represent high, high-average, low-average, and low transport rates. The four categories are bordered by the maximal, mean + 1 SD, mean, mean − 1 SD, and minimal values for the population. D/P, dialysate to plasma ratio. (Reproduced with permission from Warady et al.[34])

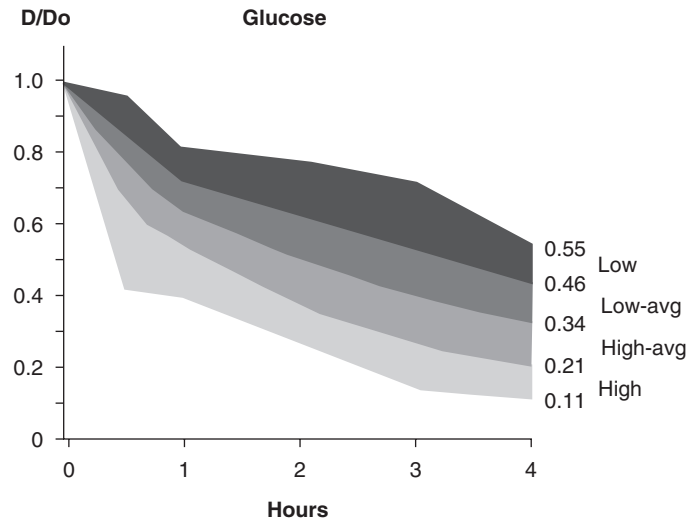

Figure 26.7 Peritoneal equilibration test results for glucose. Shaded areas represent high, high-average, low-average, and low transport rates. The four categories are boarded by the maximal, mean + 1 SD, mean, mean − 1 SD, and minimal values for the population, D/D_0, dialysate glucose to initial dialysate glucose concentration ratio. (Reproduced with permission from Warady et al.[34])

Table 26.1 The PET procedure in children

- Dwell period: 4 hours
- Fill volume: 1100 ml/m^2 BSA[a]
- 2.3–2.4% anhydrous glucose dialysis solution (Europe)
- 2.5% dextrose dialysis solution (North America, Japan)
- Test exchange after prolonged (8 hours) dwell, if possible as follows:
  - Drain the overnight dwell
  - Record the length of the dwell and the volume drained. Also note the dextrose and volume infused
  - Infuse the calculated fill volume, note infusion time
  - Keep patient in supine position
  - Drain < 10% of dialysate solution into the drain bag at 0, 120, and 240 minutes
  - Invert bag for mixing and obtain sample. Reinfuse any remaining effluent
  - Obtain blood sample after 120 minutes
- Measure creatinine and glucose in each sample
- Calculate dialysate to plasma (D/P) creatinine and dialysate glucose to baseline dialysate glucose (D/D_0) concentration ratios
- Determine transporter state by comparing creatinine and glucose equilibration curves with pediatric reference percentiles (Figures 26.6 and 26.7)

[a]In early infancy, volume may not be tolerable; in these cases, conduct PET with regular daily exchange volume for evaluation.

the dialysis prescription, a PET evaluation should be conducted soon after the initiation of dialysis.[53–55] However, there is evidence that a PET performed within the first week after the initiation of CPD may yield higher transport results than a PET performed several weeks later.[56] Accordingly, whereas it may be most convenient to perform the initial PET at the conclusion of CPD training, the results after 1 month of CPD may more accurately reflect peritoneal transport properties.[55,56]

The PET evaluation should be repeated when knowledge of the patient's current membrane transport capacity is necessary for determination of the patient's CPD prescription, especially when clinical events have occurred (e.g. repeated peritonitis) that may have altered transport characteristics. In addition, knowledge of a patient's transport capacity may have a profound impact on the overall care, because of the important relationships that exist between transport status and patient outcome in children and adults.[57–60]

Patient selection

CPD can be attempted in any child whose peritoneal cavity is intact and will admit a sufficient volume of dialysate. Experience has shown that CPD can be used successfully in children with the following conditions: polycystic kidney disease (usually after bilateral nephrectomy), prune-belly syndrome, bilateral Wilms' tumor, recent abdominal surgery (if no draining wounds are present), or with a vesicostomy, cutaneous ureterostomy, colostomy, or a ventriculoperitoneal shunt.[61–65]

CPD is the therapy of choice for the treatment of ESRD in infants.[22,66–68] Before the introduction of CPD, some pediatric dialysis programs did not accept infants for treatment of ESRD. It is now, however, widely recognized that CPD can be an effective maintenance therapy in babies who develop ESRD as early as the first few days or weeks of life.[66,69] Of course, the provision of home CPD, especially to infants, does mandate an evaluation of the patient's family by the treating facility to determine the likelihood of success, in addition to the participation of the patient's caregivers in a formal training program and an assessment of their readiness to accept the substantial responsibilities, on occasion referred to as the 'burden of care'.[70]

Finally, a successful pediatric PD program must also be able to provide the necessary multidisciplinary services required by the child and family on an ongoing basis. The services are provided by a 'team' consisting of CPD nurse specialists, nephrologists, urologists, general surgeons, renal dietitians, renal social workers, psychologists, psychiatrists, child development specialists, child life therapists, speech pathologists, and chaplains, all of whom are pediatric specialists. Children require a great investment of time and resources from the CPD team. Such an effort is often several orders of magnitude greater than that which is required to care for the typical adult CPD patient.[71]

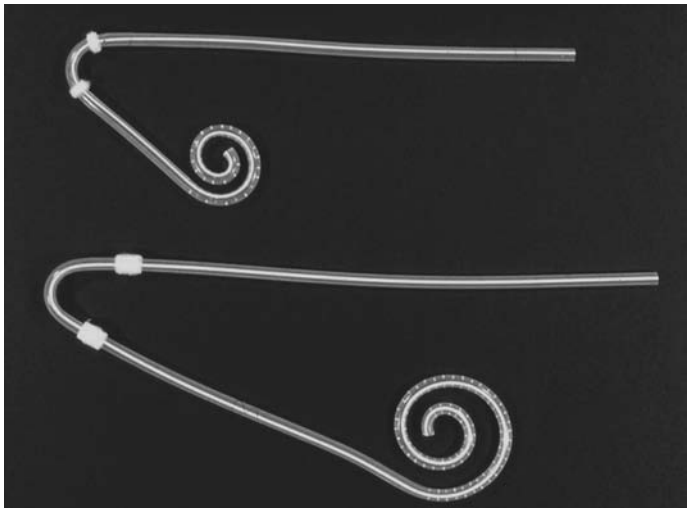

Figure 26.8 Swan-neck, double-cuff Tenckhoff peritoneal catheter with curled intraperitoneal portion.

Peritoneal dialysis access

A reliable peritoneal catheter (Figures 26.8 and 26.9) is the cornerstone of successful CPD. Goals for the PD access should include the attainment of rapid dialysate flow rates, no fluid leaks, and a low incidence of catheter-related infections.

PD catheter

In general, most long-term PD catheters are constructed of soft material, such as silicone rubber or polyurethane. The catheters can be thought of as having two separate regions, the intraperitoneal portion and the extraperitoneal portion. The intraperitoneal portion contains holes or slots to allow the passage of dialysate. The shape of the intraperitoneal portion typically is straight or curled, the latter configuration often associated with less patient pain with dialysate inflow and a decreased predisposition to omental wrapping of the catheter. The most common catheters with these characteristics used by pediatric patients have been the straight and curled Tenckhoff catheters.[72] The extraperitoneal portion of each of these catheters has one or two Dacron cuffs to prevent fluid leaks and bacterial migration and to fix the catheter's position. The shape of this portion of the catheter is also variable and may be straight or have a preformed angle (e.g. swan neck or pail handle) to help create a

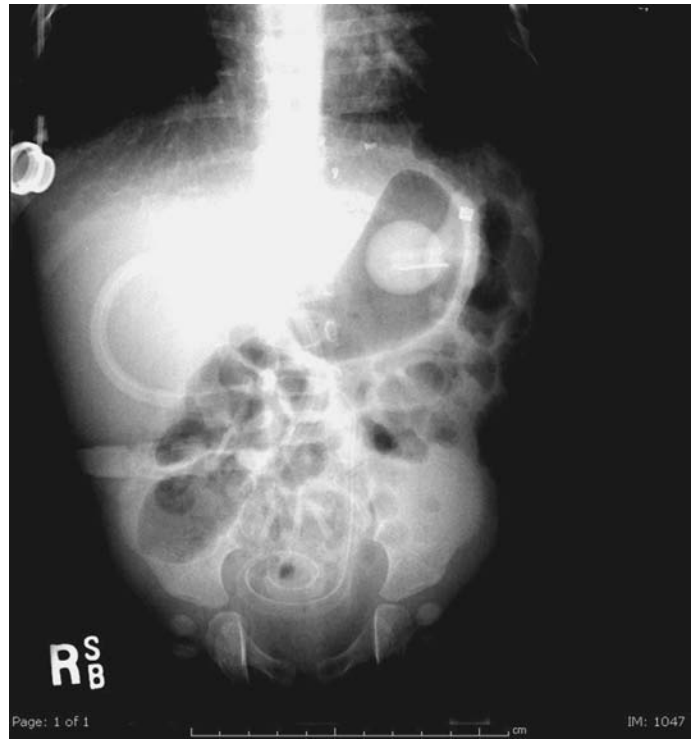

Figure 26.9 Radiologic appearance of a PD catheter location. Note the curled intraperitoneal portion within the pelvis.

downward-directed catheter exit site. The catheter characteristics themselves may influence the risk of peritonitis (see below).

Implantation site

The catheter implantation technique and the immediate postoperative care ultimately influence the longevity of the PD access. Adoption of a lateral placement technique through the body of the rectus muscle has resulted in a decrease in catheter leakage.[73] While there is limited experience with laparoscopic placement of PD catheters in children, the technique may result in rapid postoperative recovery and greater catheter longevity.[74] Irrespective of the implantation procedure, the catheter exit site should be directed downward and the provision of preoperative antibiotics is recommended because of the association between antibiotic usage and a decreased incidence of postoperative peritonitis.[75] Most current recommendations suggest the use of a first-generation cephalosporin in adults and children at the time of catheter placement.[76–78]

It is believed that infants and young children with a vesicostomy, ureterostomy, or colostomy may benefit from placement of the catheter exit site as far from the stoma as possible to prevent contamination and infection. Placement of the exit site on the chest wall and with a downward orientation has successfully limited the number of infections in such high-risk situations in a small number of children and adults.[72,79–81]

Immediate postoperative care

Following catheter insertion, catheter immobilization is imperative to prevent trauma to the healing exit site, but exit-site sutures should not be placed due to the risk of subsequent infection. Whenever possible, a delay of 10–15 days prior to using the chronic catheter is desirable to allow for completion of healing. Ideally, exit-site care conducted during the immediate postoperative period should be performed weekly with mask and gloves and should be conducted by trained dialysis staff. The initial low frequency of dressing changes is designed to prevent contamination of the exit site with bacteria and to decrease the likelihood of manipulation of the catheter, which increases the risk of exit-site trauma.[82] The exit site should be cleansed with a non-irritating agent such as poloxamer 188 and, ideally, the exit site should be evaluated weekly for the quality of healing over a 6-week period.

Long-term care

There is little consensus regarding the optimal approach to long-term exit-site care after healing is complete. It does appear, however, that cleansing the exit site with soap and water is as effective as using oxidants such as povidone iodine and hydrogen peroxide, both of which can be cytotoxic to mammalian cells.[83,84] After cleansing, the exit site should be patted dry with a sterile gauze and the catheter should be well immobilized. Most pediatric patients are prescribed a dressing over the exit site which is changed as part of daily or every other day exit-site care.

Complications of peritoneal dialysis

Peritonitis

The single most common complication that occurs in children maintained on CPD is peritonitis.[73,76,77,85–89] Present data make it clear that children have a significantly greater rate of peritonitis than adults, with a substantial number of children experiencing an episode of peritonitis during their first year of CPD treatment.[90] Reductions in observed peritonitis rates have been reported in both adults and children in association with treatment of *Staphylococcus aureus* nasal carriage, as well as with recent technical developments such as newer disconnect systems and the flush-before-fill technique.[76,88,91–95] The important contribution of prolonged dialysis training has also been demonstrated.[96]

Incidence

Recent NAPRTCS data on 3617 episodes of peritonitis has revealed an annualized peritonitis rate of 0.64 or 1 infection every 18.6 patient months.[22] The rate of peritonitis was highest in the youngest patients (0–1 years old) who had an annualized peritonitis rate of 0.79 or 1 infection every 15.2 months in contrast to an annualized rate of 0.61 or 1 episode every 19.6 patient months in children more than 12 years old. In this same report, the annualized peritonitis rate was noted to be best in association with Tenckhoff catheters with straight intraperitoneal segments, double-cuffs, swan-neck tunnels, and downward-pointed exit sites.

Infecting organisms

Gram-positive peritonitis accounts for 50% of the episodes and is most frequently due to coagulase-negative staphylococcus. Gram-negative peritonitis is caused by a wide variety of organisms, and yeasts (e.g., *Candida* spp.) are the most common fungal organisms causing peritonitis.[97]

Treatment

The current approach to the treatment of bacterial peritonitis relies primarily on the intraperitoneal administration of antibiotics (Table 26.2). A key development has been the publication of the 'Consensus Guidelines for the Treatment of Peritonitis in Pediatric Patients Receiving Peritoneal Dialysis' under the auspices of the International Society of Peritoneal Dialysis.[98] This set of 15 guidelines includes recommendations for empiric antibiotic therapy as well as for treatment of Gram-positive and Gram-negative peritonitis (Figures 26.10–26.12).

The most crucial element in the treatment of fungal peritonitis is removal of the PD catheter.[99] The duration of antifungal treatment following catheter removal should be 2 weeks

Table 26.2 Antibiotic dosing recommendation; administration should be via the intraperitoneal route unless specified otherwise

	Continuous therapy		
	Loading dose[a]	Maintenance dose	Intermittent therapy[b]
Glycopeptides[c]			
Vancomycin	500 mg/L	30 mg/L	30 mg/kg q 5–7 days
Teicoplanin[d]	200 mg/L	20 mg/L	15 mg/kg q 5–7 days
Cephalosporins			
Cefazolin/cephalothin	250 mg/L	125 mg/L	15 mg/kg q 24 h
Cefuroxime	200 mg/L	125 mg/L	15 mg/kg q 24 h
Cefotaxime	500 mg/L	250 mg/L	30 mg/kg q 24 h
Ceftazidime	250 mg/L	125 mg/L	15 mg/kg q 24 h
Ceftizoxime	250 mg/L	125 mg/L	–
Antifungals			
Amphotericin B	1 mg/kg IV	1 mg/kg/day IV	–
Fluconazole	–	–	3–6 mg/kg IP, IV, or PO q 24–48 h
Flucytosine	50 mg/kg IV or PO (max dose 2.0 g)	25–37.5 mg/kg PO q 24 h (max dose 1.0 g)	(max dose 200 mg) –
Aminoglycosides[e]			
Amikacin	25 mg/L	12 mg/L	–
Gentamicin	8 mg/L	4 mg/L	–
Netilmycin	8 mg/L	4 mg/L	–
Tobramycin	8 mg/L	4 mg/L	–
Penicillins[e]			
Azlocillin	500 mg/L	250 mg/L	–
Piperacillin	–	250 mg/L	150 mg/kg IV q 12 h
Ampicillin	–	125 mg/L	–
Oxacillin	–	125 mg/L	–
Nafcillin	–	125 mg/L	–
Amoxicillin	250–500 mg/L	50 mg/L	–
Quinolones			
Ciprofloxacin	50 mg/L	25 mg/L	–
Combinations			
Ampicillin/sulbactam	1000 mg/L	100 mg/L	–
Imipenem/cilastatin	500 mg/L	200 mg/L	–
Trimethoprim			–
Sulfamethoxazole	320/1600 mg/L	80/400 mg/L	
Others			
Clindamycin	300 mg/L	150 mg/L	–
Metronidazole	–	–	15 mg/kg/day PO, IV or rectally in 3 doses (max dose 1.5 g/day)
Rifampin	–	–	20 mg/kg/day PO (max dose 600 mg/day)
Aztreonam	1000 mg/L	250 mg/L	–

q = every; IV = intravenously; IP = intraperitoneally; PO = orally.

[a]Loading dose should be administered during a standardized 3- to 6-hour dwell period. Concentration-related loading doses assume usual patient-specific fill volume (i.e. approximately 1100 ml/m^2 body surface area). If a smaller volume is instilled, the concentration must be increased to ensure infusion of an equal mass of antibiotic.

[b]Intermittent antibiotic dosing should be administered over ≥6 hours in one bag per day for CAPD patients, or during a full fill volume daytime dwell for APD patients, unless otherwise specified.

[c]Accelerated glycopeptide elimination may occur in patients with residual renal function. If intermittent therapy is used in this setting, the second dose of antibiotic should be time-based on a blood level obtained 3–5 days after the initial dose. Redosing should occur when the blood level is <12 mg/L for vancomycin, or 8 mg/L for teicoplanin. Intermittent therapy is not recommended for patients with residual renal function unless serum drug levels can be monitored in a timely manner.

[d]Teicoplanin is not currently available in the United States.

[e]Aminoglycosides and penicillins should not be mixed in dialysis fluid because of the potential for inactivation.

Table reproduced with permission from Oh et al.[94]

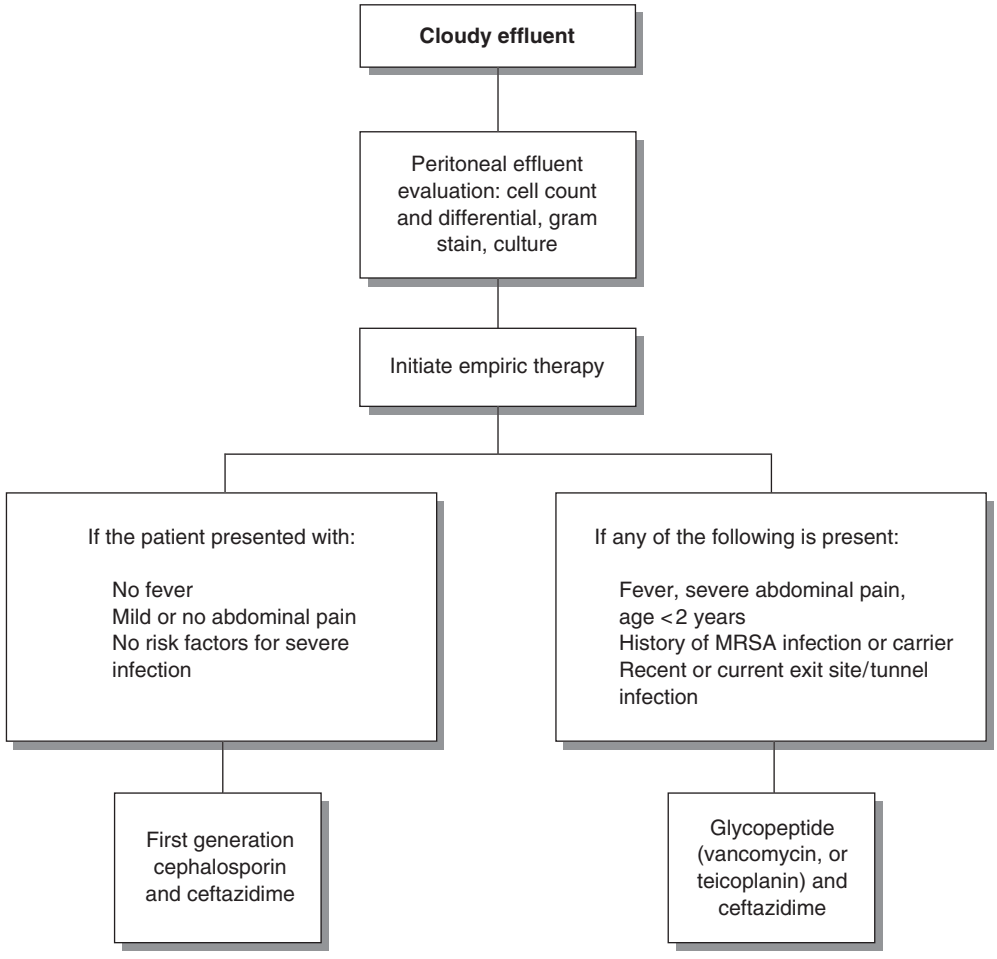

Figure 26.10 Empiric therapy of peritonitis. (Reproduced with permission from Warady et al.[98])

or longer following complete resolution of the clinical symptoms of infection.[98] Whereas amphotericin B has generally been recommended as medical therapy, the peritoneal penetration of amphotericin B with systemic administration is poor. On the other hand, fluconazole is characterized by excellent bioavailability and peritoneal penetration and is currently the drug of choice for most *Candida* spp.[100–102]

The International Pediatric Peritonitis Registry (IPPR) is currently accumulating outcome data following the application of these guidelines into clinical care with plans to generate evidence-based prevention and treatment guidelines in 2005. Preliminary data have revealed a 92% success rate for peritonitis treatment performed in accordance with the guidelines.[103,104]

Sclerosing encapsulating peritonitis

Sclerosing encapsulating peritonitis (SEP) is a rare but extremely serious clinical entity characterized by the presence of continuous, intermittent, or recurrent bowel obstruction associated with gross thickening of the peritoneum.[105–107] Although primarily diagnosed in adults, it may also occur in children, typically those who have received CPD for >5 years. The presence

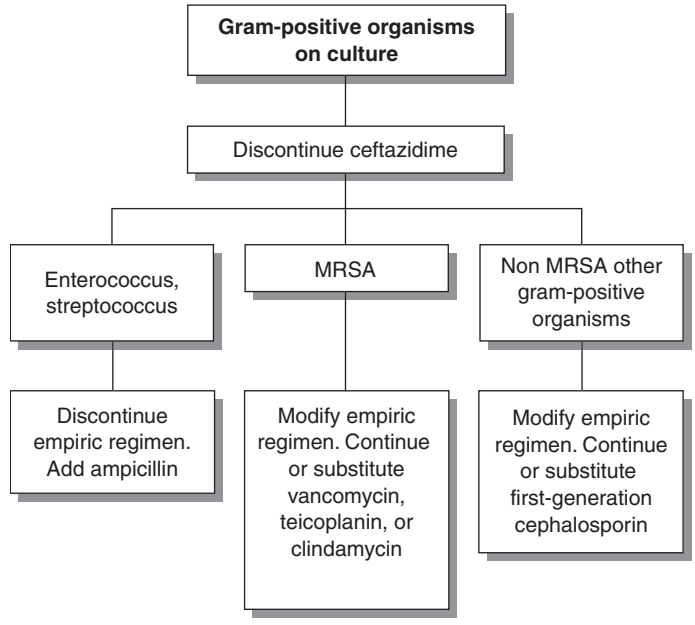

Figure 26.11 Treatment of peritonitis with gram-positive organisms on culture. (Reproduced with permission from Warady et al.[98])

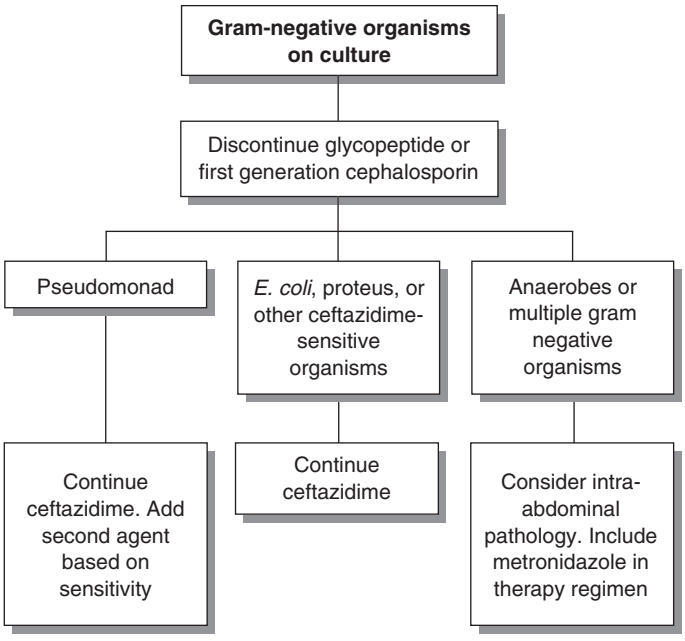

Figure 26.12 Treatment of peritonitis with gram-negative organisms on culture. (Reproduced with permission from Warady et al.[98])

of peritoneal calcifications on abdominal computed tomography (CT) scan in association with ultrafiltration failure is highly suggestive of the diagnosis and may be an indication to discontinue CPD.

Exit site and tunnel infection

Catheter exit-site and tunnel infections, most often secondary to *Staphylococcus* or *Pseudomonas infection*, are associated with a significantly increased risk for the development of peritonitis.[108–110] As noted previously, the initial approach to prevention occurs at the time of catheter placement, usually in the form of a single dose of a first-generation cephalosporin, unless the patient is known to be colonized with a methicillin-resistant organism.[75–78,98] Preventive measures should continue in the immediate postoperative period and should ideally include the delayed (2–6 weeks) initiation of dialysis to facilitate wound healing and minimize the risk of dialysate leakage. The catheter should also be securely immobilized without the use of surgical sutures.

Attention to *S. aureus* nasal carriage in patients on CPD is recommended, as a substantial body of literature supports an association between nasal carriage and the development of catheter-related infections and peritonitis.[76–78,111] In families of pediatric CPD patients, concern related to *S. aureus* nasal carriage extends to caretakers, since as many as 45% of families with children on CPD have been found to have one or more members with evidence of nasal carriage.[92] The use of mupirocin, intranasally or at the catheter exit site, has been associated with a decreased rate of exit site infections.[77,111,112] Most recently, the occasional development of a *Pseudomonas* exit-site infection in association with mupirocin usage has prompted a recommendation for the prophylactic application of gentamicin ointment usage instead, by some investigators.[113]

Prompt diagnosis and effective therapy of exit-site/tunnel infections are also crucial elements of peritonitis prevention measures. Objective criteria for diagnosis have been developed based on experiences in children and adults and it needs to be emphasized that the isolation of a pathogen is not necessary if the clinical findings of an infection are readily apparent.[98]

Once diagnosed, antibiotic therapy should be chosen according to the susceptibilities of the cultured organism. The duration of treatment should be for 2–4 weeks, and at least 7 days following complete resolution of the infection.[114]

Hernia

The incidence of hernias in children on PD is inversely proportional to the patient's age; the highest frequency of inguinal hernias occur in patients < 1 year of age.[115,116] More than 75% of hernias do require surgical repair, a procedure that typically is followed by no/low volume dialysis for several days. Although there appears to be a relationship between intraperitoneal pressure and hernia development in children, the IPP per infused dialysate volume is regularly less than that experienced by adults.[117]

Fluid Leaks

Fluid leaks can occur early after catheter implantation (< 30 days) and typically present at the catheter exit site.[118] In contrast, later leaks can manifest as abdominal wall/genital edema or scrotal swelling.[119] The diagnosis of a fluid leak is typically made by detecting the high glucose content of dialysate from fluid found at the exit site, or by radiologic imaging after instilling a radionuclide/contrast agent into the peritoneal fluid.[116] Whereas leaks may be managed in some patients by the use of smaller exchange volumes, a change from CAPD to APD and overnight cycling, or possibly catheter revision, prevention is preferable. This may be best achieved by the delayed initiation of PD following catheter placement and the possible application of fibrin glue at the deep cuff at the time of catheter implantation.[120]

Hydrothorax

Hydrothorax, or the accumulation of dialysis fluid within the pleural space, is yet another complication associated with the presence of an increased IPP. The absence of muscle fibers in the diaphragm or diaphragmatic eventration predisposes to the relocation of dialysis fluid.[121,122] A hydrothorax may be detected incidentally on routine radiograph or may manifest soon after the initiation of PD as acute respiratory distress. The hydrothorax is usually on the right side, quite possibly as a result of the heart

and pericardium preventing fluid movement across the left hemidiaphragm.[123] In addition to the physical examination and chest X-ray, the diagnosis of a hydrothorax may be made by thoracentesis and detection of fluid with the characteristic high glucose content of dialysate or by scintigraphy. The subsequent continuation of PD has occurred following temporary cessation of PD (and the institution of hemodialysis), the use of APD and small nocturnal exchange volumes associated with a lower IPP, or obliteration of the pleural space with a variety of materials.[119,124,125] In those instances where a clear anatomic defect is noted, operative repair is characteristically successful.[126]

Peritoneal dialysis adequacy

Providing adequate dialysis solute clearance requires the physician to be cognizant of the patient's BSA, peritoneal membrane solute transport capacity (as determined by the PET), and residual renal function (RRF) when designing the dialysis prescription (Figure 26.13).[53,127–129] Most studies in adult CPD patients where clinical outcome parameters have been monitored have characterized dialysis adequacy in terms of solute removal as a total (RRF + peritoneal dialysis) weekly $Kt/V_{urea} \geq 2.0$ and/or a total weekly creatinine clearance $\geq 60\,L/1.73\,m^2$ for the patient receiving CAPD who is a high or a high-average transporter, and a creatinine clearance $\geq 50\,L/1.73\,m^2$ for low or low-average transporters. Although minor differences in the recommendations exist for the automated cycler dialysis patients, a recent study of adults has provided data that challenge current PD adequacy recommendations.[55,130] Whereas current clinical experience supports the use of similar (or greater) target clearances for children, the soon to be published revision of the K/DOQI PD Adequacy Guidelines will emphasize that the assessment of a patient's clinical status is an additional important measure of dialysis adequacy.

The calculation of the total weekly creatinine clearance (CCR) is performed in the following manner:

$$C_{Cr}[L/1.73m^2/week] = \left\{\frac{D_{cr} \times V_D}{P_{cr}} + \left[\left(\frac{U_{cr} \times V_U}{P_{cr}} + \frac{U_{ur} \times V_U}{P_{ur}}\right) \Big/ 2\right]\right\} \times \frac{1.73}{BSA} \times 7$$

where D_{cr}, P_{cr}, and U_{cr} are the dialysate, plasma, and urinary concentrations of creatinine, U_{ur} and P_{ur} the urinary and plasma concentrations of urea, V_D and V_U the 24-hour dialysate and urine volumes, and BSA the body surface area.

The total weekly Kt/V_{urea} is calculated as follows:

$$\text{Weekly } Kt/V_{urea} = \frac{(D_{ur} \times V_D)(U_{ur} \times V_U)}{P_{ur} \times V} \times 7$$

where D_{ur}, U_{ur}, and P_{ur} are the dialysate, urinary, and plasma concentrations of urea, V_D and V_U the 24-hour dialysate and urine volumes, and V the urea distribution volume.

In the calculation of Kt/V_{urea}, it is most important to use an accurate estimate of V, which is considered to be equivalent to the total body water volume.[131,132] Several computer-based dialysis modeling programs have been validated in children and can assist the prescription process.[25,133]

Despite our increasing ability to accurately measure solute removal, there are few data to support the preference of one solute clearance measure (Kt/V_{urea} vs creatinine clearance) over another, and discrepancies in the results may occur in as many as 20% of patients. This has prompted the recommendation that the evaluation of adequacy be based on the results of both clearance measures and, most importantly, on an ongoing assessment of the patient's clinical condition, including the volume status of the patient.[134–136] As suggested previously, any reference to dialysis adequacy in children should ideally always take into account issues such as growth, nutritional status, cardiovascular status, management of anemia, and control of secondary hyperparathyroidism.

Outcome

An assessment of patient outcome must take into account short-term and long-term measures. Recent data have been generated related to the health-related quality of life (HRQOL) of children with ESRD and in the two most recent studies evidence has been collected which reveals the HRQOL of children on dialysis to be inferior to that of children with a successful kidney transplant. The presence of anemia may also contribute to a suboptimal HRQOL.[137,138]

Anemia has also been shown to be associated with an increased risk for hospitalization and patient mortality in children initiating dialysis. In fact, the risk of mortality was increased by 80% in those patients with a hematocrit of <27% vs those whose hematocrit was >33%.[139] In a recent annual report of the NAPRTCS, an overall mortality rate of 8.5% was noted for the pediatric PD population.[140] An assessment related to age revealed a mortality rate of 14.9% for patients < 5 years of age at dialysis initiation, which was significantly greater than the mortality rates of 5.7% and 4.5% for patients in the 6–12 and >13 year age groups, respectively. The primary reported causes of death for all PD patients were infection (27.9%) and cardiopulmonary disease (20.9%). Finally, these statistics corroborate the worrisome data generated by the USRDS, which recently reported a significantly worse 5-year patient survival for pediatric dialysis patients compared with the transplant population.[18] In fact, the expected remaining lifetime (years) for incident ESRD patients from 0–14 years of age on dialysis was only 20.1 years in comparison to 49.5 years for the transplant population of the same age and 67.9 years for 10-year-old patients in the general population. These data emphasize that, irrespective of the positive aspects of dialysis, one should aim to minimize the time a child spends on dialysis prior to transplantation whenever possible.

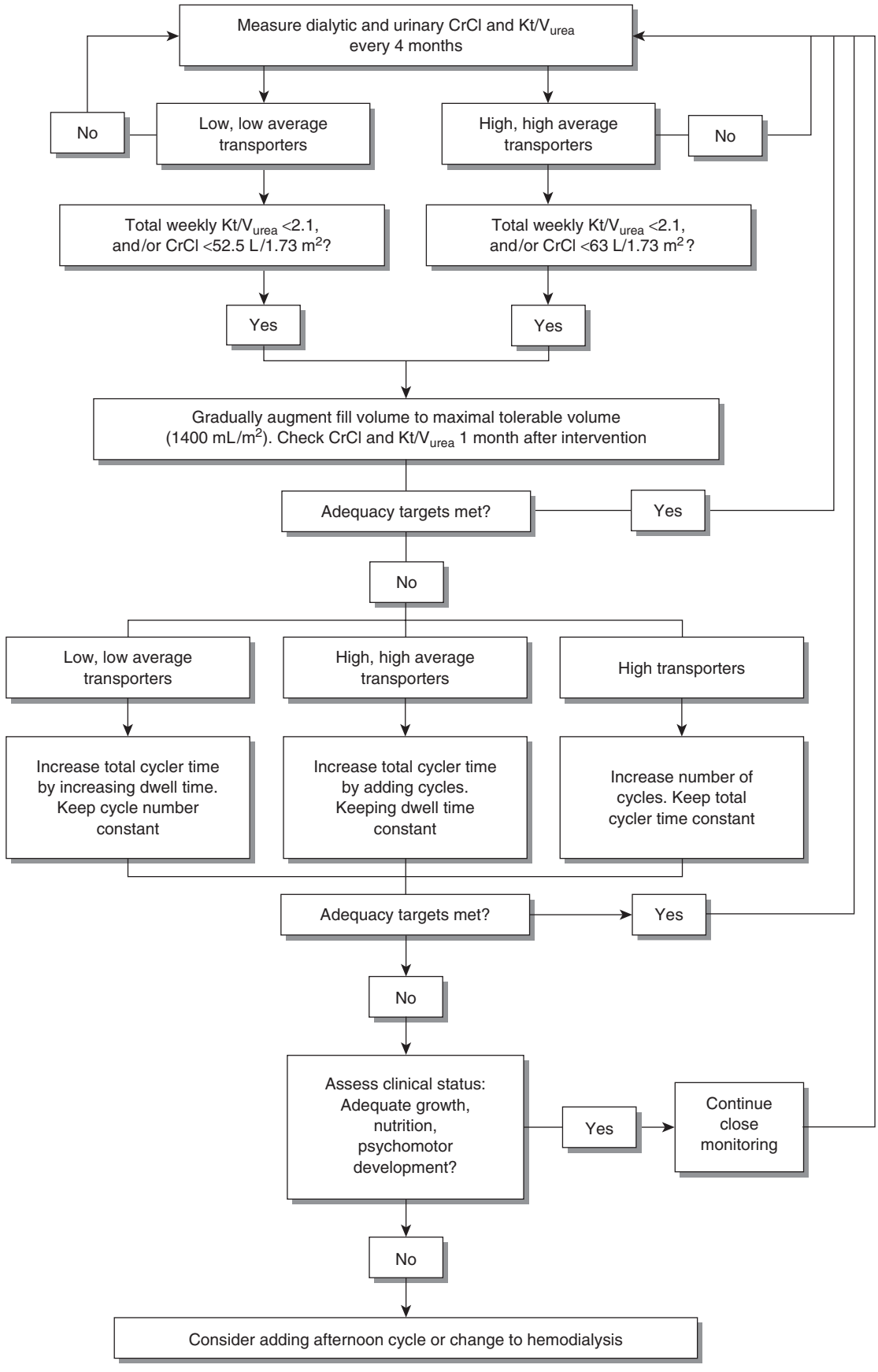

Figure 26.13 Maintenance PD prescription in APD.

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27 Continuous renal replacement therapy

Timothy E Bunchman and Kevin D McBryde

Continuous renal replacement therapy (CRRT) has changed in the last three decades from an experimental modality to the accepted standard of care for hemodynamically unstable, critically ill pediatric and adult patients.[1–4] As a result, CRRT has become the treatment of choice for critically ill patients, with diagnoses ranging from volume overload to acute renal failure and complex multi-organ dysfunction syndrome (MODS).[5]

Historical perspective

In 1977, Kramer et al demonstrated the efficacy of a unique system for ultrafiltration in patients with fluid overload.[6] The device consisted of a capillary hemofilter and utilized the systemic arterial blood pressure to drive ultrafiltration. This novel technique, termed continuous arteriovenous hemofiltration (CAVH), was initially adopted as a technology independent alternative to hemodialysis. Over the last 25 years, the technology introduced by Peter Kramer has evolved, and has been modified further to provide both convective as well as diffusive exchange of solutes for enhanced solute clearance. In order to achieve predictable and controlled ultrafiltration, pump-assisted systems were developed in the early 1990s and replaced arterial blood pressure-driven systems. This pump-assisted technique has come to be known as continuous venovenous hemofiltration (CVVH). In the last decade, elaborate CVVH devices with added safety, ultrafiltration, and thermal control mechanisms have been introduced in clinical practice. These devices are a far cry from the simple design envisioned by Peter Kramer.

Indications and applications of CRRT

In general, indications for initiating CRRT in children and adults are similar (Table 27.1). The most common clinical use of CRRT is in the treatment of acute renal failure (ARF) and fluid overload. The unique applications for CRRT in the

Table 27.1 Indications (AEIOUM) for initiation of CRRT

Acute severe metabolic acidosis (A)

Electrolyte abnormalities (E)
Hyperkalemia
Hypernatremia
Hypo-/hypercalcemia
Hypo-/hyperphosphatemia

Intoxications (I)
Low molecular weight, not protein-bound:
- Gentamicin
- Lithium
- Ethylene glycol
- Methanol
- Ethanol
- Salicylates
- Acetaminophen

High molecular weight, protein-bound:
- Vancomycin
- Phenobarbital
- Carbamazepine
- Theophylline

Fluid overload (O)
Pulmonary edema not responsive to diuretics
Oliguria
Anuria

Uremia (U)

Miscellaneous (M)
Tumor lysis syndrome
Hyperosmolality
Coagulopathy and need for large volumes of blood products combined with ARF
Uncontrolled hyperthermia – core temperature >39.5°C

Inborn errors of metabolism:
- Urea cycle defects
- Branched-chain amino acidurias

Lactic acidosis

pediatric population include support of patients receiving extracorporeal membrane oxygenation (ECMO) and of patients with inborn errors of metabolism.

The chief advantage of CRRT is its ability to allow correction of metabolic disorders, and fluid and electrolyte disturbances, while minimally impacting hemodynamic stability in sick patients (Table 27.2). Consequently, CRRT is often considered as the therapy of choice for the critically ill patients who may be hemodynamically unstable, or for those patients who would not be considered optimal candidates for either intermittent hemodialysis or peritoneal dialysis. Since CRRT is a continuous therapy conducted over longer time, the overall solute clearance achievable with this modality can be superior to intermittent hemodialysis.[7–10] The slow and continuous clearance of solutes in CRRT is isotonic and is considered more physiologic, lessening the likelihood of rapid metabolic shifts and dysequilibrium syndrome.

Successful application of CRRT requires that patients be connected to an extracorporeal circuit for prolonged periods and remain immobilized. This is especially important in small children, who may require sedation in order for the procedure to be conducted safely. The CRRT procedure necessitates the placement of an appropriate-sized intravascular catheter, which can be associated with its own risks, such as bleeding and injury to other organs. The CRRT circuits also require the use of anticoagulation, thereby enhancing the risks of systemic bleeding. Many CRRT circuits lack a blood-warming mechanism, which can cause hypothermia, especially in infants.

Definitions

Continuous arteriovenous hemofiltration

In early descriptions of CRRT, blood was pumped through the extracorporeal circuit by the patient's own arterial blood pressure. An artery cannulated to provide arterial access, and the blood was returned to the patient via a venous access. Such a system is described as an arteriovenous system. Infusion of replacement fluid into the vascular space, either in pre- or posthemofilter position, in the arteriovenous configuration, is referred to as continuous arteriovenous hemofiltration or CAVH (Figure 27.1A).

Table 27.2 Advantages and disadvantages of CRRT

Advantages	Disadvantages
Hemodynamic stability	Need for intravascular access
Slow fluid and solute removal	Need for anticoagulation
Greater solute clearance (Kt/V)	Need for patient immobilization
Runs continuously	Nutritional clearance
ICU nurses troubleshoot the machines	Higher cost

Continuous arteriovenous hemodialysis
If a counter-current dialysate is pumped through the hemofilter and no replacement solution is infused, then the system is considered continuous arteriovenous hemodialysis, or CAVHD (Figure 27.1B)

Continuous arteriovenous hemodiafiltration
If a combination of countercurrent dialysate and pre- or postfilter replacement fluid is utilized, then the CRRT system is considered to be continuous arteriovenous hemodiafiltration, or CAVHDF (Figure 27.1C).

Continuous venovenous hemofiltration

Unfortunately, the majority of patients who require CRRT are hemodynamically unstable, and thus their endogenous blood pressure is often inadequate to provide sufficient blood flow to the extracorporeal system. However, the use of roller pumps to provide both the arterial and venous blood flows has been utilized in the design and manufacture of the newest generation of CRRT machines. Thus, these CRRT machines require only a double-lumen access into the venous circulation in order to withdraw and subsequently infuse the patient's blood into the CRRT machine. This is known as a continuous venovenous system. As before, the use of replacement solutions in these systems constitutes a continuous venovenous hemofiltration system, or CVVH (Figure 27.1A).

Continuous venovenous hemodialysis
Use of dialysate constitutes a continuous venovenous hemodialysis, or CVVHD system (Figure 27.1B).

Continuous venovenous hemodialysis
Concurrent replacement fluid and dialysate in these machines is described as continuous venovenous hemodiafiltration, or CVVHDF (Figure 27.1C).

Slow continuous ultrafiltration
If neither a replacement nor dialysate solution is utilized, and the CRRT circuit is used to merely ultrafilter plasma, then the procedure is considered to be slow continuous ultrafiltration or SCUF (Figure 27.1D), and this may be achieved with either a continuous arteriovenous or continuous venovenous system.

Diffusion and convection

Ion transport and exchange in the CRRT is achieved by both diffusion and convection. Diffusion, simply put, is the transfer of solute across a semipermeable membrane from an area of high concentration to an area of low concentration (Figure 27.2A).[7–9] Diffusion movement is directly proportional

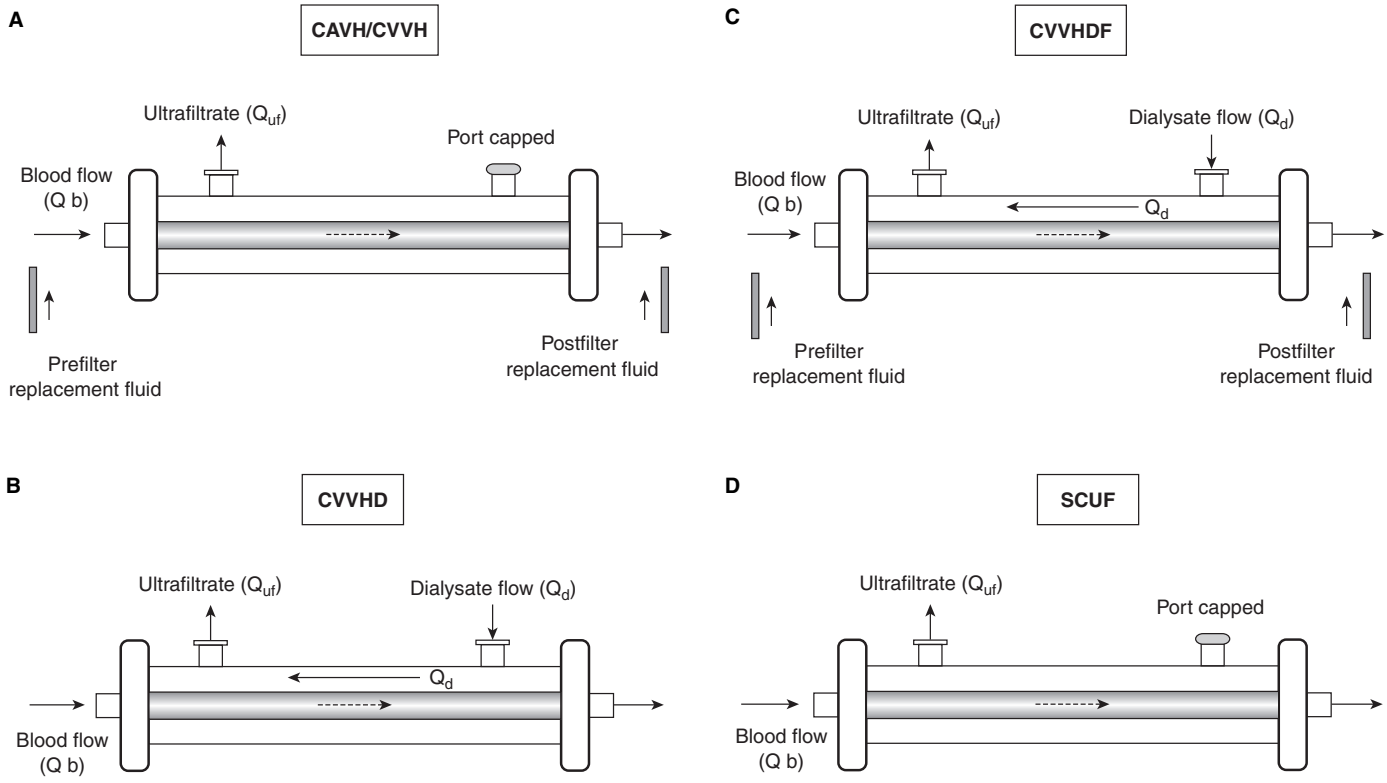

Figure 27.1 CRRT modalities. (A) Hemofiltration (CAVH or CVVH); (B) hemodialysis (CAVHD or CVVHD); (C) hemodiafiltration (CAVHDF or CVVHDF); and (D) slow continuous ultrafiltration (SCUF).

to the diffusive coefficient of the solute, the temperature, the surface area of the interface, the concentration gradient, and the distance to traverse across the membrane.[7] Diffusion is effective at clearing small molecular weight solutes, but clearance decreases with increasing molecular weight.[9]

In contrast, convection is the transfer of solute across a semipermeable membrane in association with a significant amount of water across the membrane (Figure 27.2B).[7–9] In other words, water moves across the semipermeable membrane and 'drags' solute with it.[8] Ultrafiltration is the process by which plasma water and plasma solutes are separated from whole blood by the application of a transmembrane pressure across a semipermeable membrane.[7]

CRRT devices

Several devices are now available commercially for CRRT (Figures 27.3A–D). Simplified mechanics of these devices and the CRRT extracorporeal circuit are shown in Figure 27.4. In essence, the patient's blood is drawn into the hemofilter through a blood tubing connected to the patient's central venous access. An 'arterial' pump facilitates drawing of blood from the arterial side of the vasular access into the extracorporeal circuit. The 'arterial' pump also generates the hydrostatic pressure necessary for ultrafiltration in the hemofilter. Following ultrafiltration and convective solute exchange in the hemofilter, the blood is returned to the patient through the 'venous' side of the vascular access. Some CRRT devices have a pump in the 'venous' side of the extracorporeal circuit in order to control the flow of blood in the circuit.

The dialysate used for diffusive solute clearance is pumped into the hemofilter via its side-port. The dialysate is separated from the blood by the hemofilter capillary membrane and flows in a countercurrent path to the flow in the blood column. Flow of the dialysate into the hemofilter is controlled with a pump. Replacement fluid is administered into the extracorporeal circuit at the prehemofilter, or the posthemofilter location using another pump.

Pulsatile or piston-action intravenous (IV) pumps were used in early versions of CRRT devices in order to control the ultrafiltration rate during the procedure. These pumps can have an error rate of up to 30%, are inaccurate for control of ultrafiltration, and can lead to complications.[11] Ultrafiltration control error in the newer CRRT devices is only 1–2% of total ultrafiltration, resulting in a better control of therapy goals.

Hemofilter

Hemofilters used in CRRT are similar in design to hemodialyzers, except that the filter capillaries have significantly higher hydraulic permeability. Some CRRT devices permit interchangeability of hemofilters with varying size and permeability

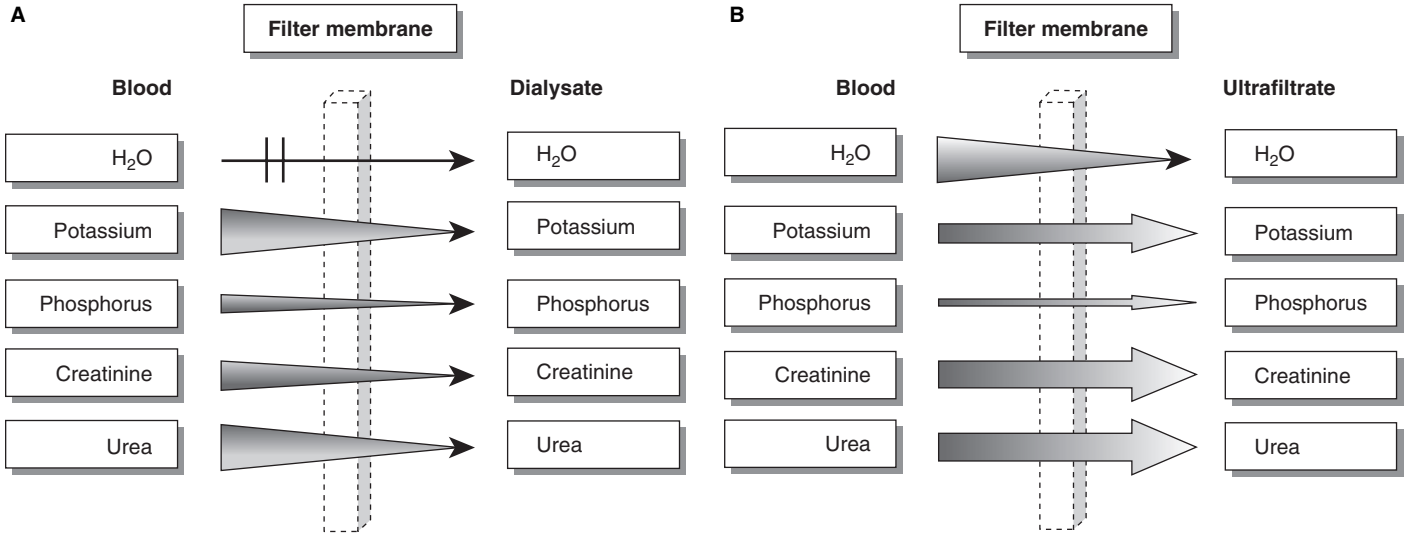

Figure 27.2 A conceptual drawing of the principles of diffusive and convective clearance. (A) Diffusion: solutes move down their concentration gradient, from the compartment of high concentration to the compartment of low concentration. In pure diffusion, there is no net movement of water. Small molecular-weight molecules (e.g. potassium and urea) move rapidly (wide arrows) and medium molecular weight molecules (e.g. creatinine and phosphorus) move more slowly (narrowed arrows) across the semipermeable membrane. (B) Convection: solutes are pulled across the semipermeable membrane by the movement of water. Solutes move across the semipermeable membrane without any shift in osmolality. In pure convection, there is primarily a net movement of water. Arrow width indicates relative transport of solutes.

characteristics, whereas other devices require the use of specific hemofilter sets.

Vascular access

Success of CRRT is vastly dependent on the adequacy of vascular access. Therefore, a considerable thought must be given to the selection of site for insertion, as well as size and type of arteriovenous (AV) access in each patient who is to begin a CRRT.

Potential sites for placement of the AV access include the internal jugular vein, the subclavian vein, and the femoral vein. Because of lower risk of vascular stenosis and pneumothorax, and its large size, the internal jugular site is a preferred site for placement of AV access. Additionally, the internal jugular vein site allows for easier rehabilitation of the patient while receiving renal replacement therapy. The femoral vein is a relatively large vessel and is also often used as an access for CRRT. However, longer catheters with more 'dead-space' may be necessary for the tip of the access to reach the common iliac vessel or the inferior vena cava. The subclavian vessel is often the least used, due to the risk of pneumothorax associated with placement of the catheter. The size of the vascular access should be proportional to the size of the patient (Table 27.3).

Blood flow rate

A minimum blood flow rate (BFR) of 30–50 ml/min, and ideally a blood flow rate of 400 ml/min/1.73 m^2, should be targeted for successful CRRT. This blood flow rate approximates to 10–12 ml/kg/min in infants, 4–6 ml/kg/min in children, and 2–4 ml/kg/min in adolescents. Maximum achievable BFR varies with the CRRT device used.

Dialysate solutions for CRRT

At its inception, replacement or dialysate solutions used in CRRT were lactate-based, such as peritoneal dialysis solutions or Ringer's lactate. Increased plasma lactate concentrations have been reported with the use lactate-based solutions, especially in patients with acute hepatic failure.[12–15] Hemodynamic instability and poor cardiac performance have been reported in the patients undergoing CRRT with lactate-based dialysate.[14,15]

In contrast, bicarbonate-based dialysate has been shown to result in a significant increase in the arterial pH and a decrease in the base deficit, as well as a trend towards a greater cardiac index, a lower infusion rate of dobutamine, and high oxygen delivery.[16,17] Distinct advantages of bicarbonate-based dialysate in improving cardiovascular functions in CRRT have been further described in other clinical studies.[18–20] Because of better acid–base balance and improved cardiovascular functions, bicarbonate-based dialysate and replacement solutions are now recommended as the standard of care for CRRT. Normocarb (Dialysis Solutions, Inc., Richmond Hills, Ontario), a bicarbonate-based dialysate solution, has been available commercially for use in CRRT since 2000.[21] Further, work by our group has shown that Normocarb can be a safe alternative as a replacement solution for convective solute clearance.[22]

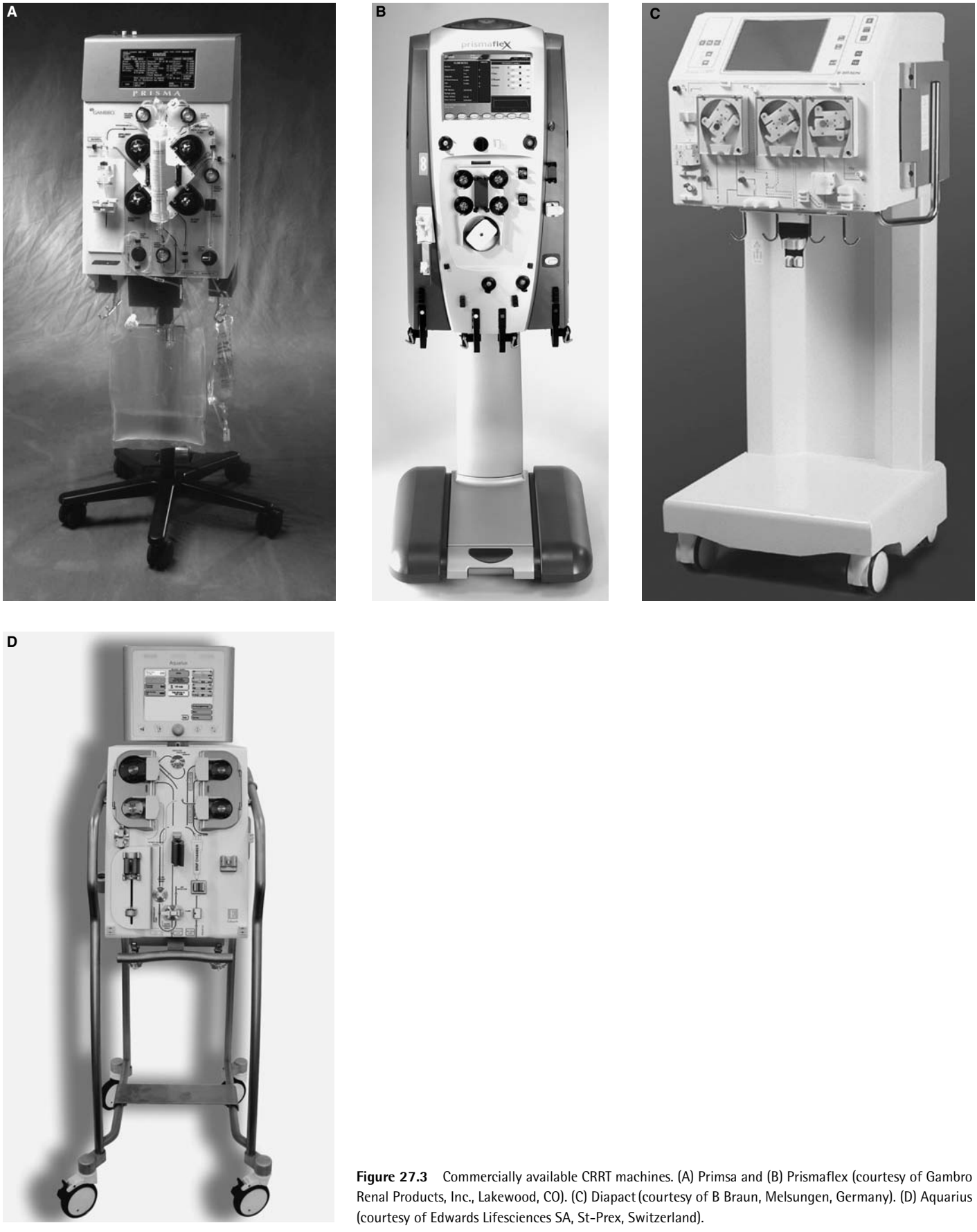

Figure 27.3 Commercially available CRRT machines. (A) Primsa and (B) Prismaflex (courtesy of Gambro Renal Products, Inc., Lakewood, CO). (C) Diapact (courtesy of B Braun, Melsungen, Germany). (D) Aquarius (courtesy of Edwards Lifesciences SA, St-Prex, Switzerland).

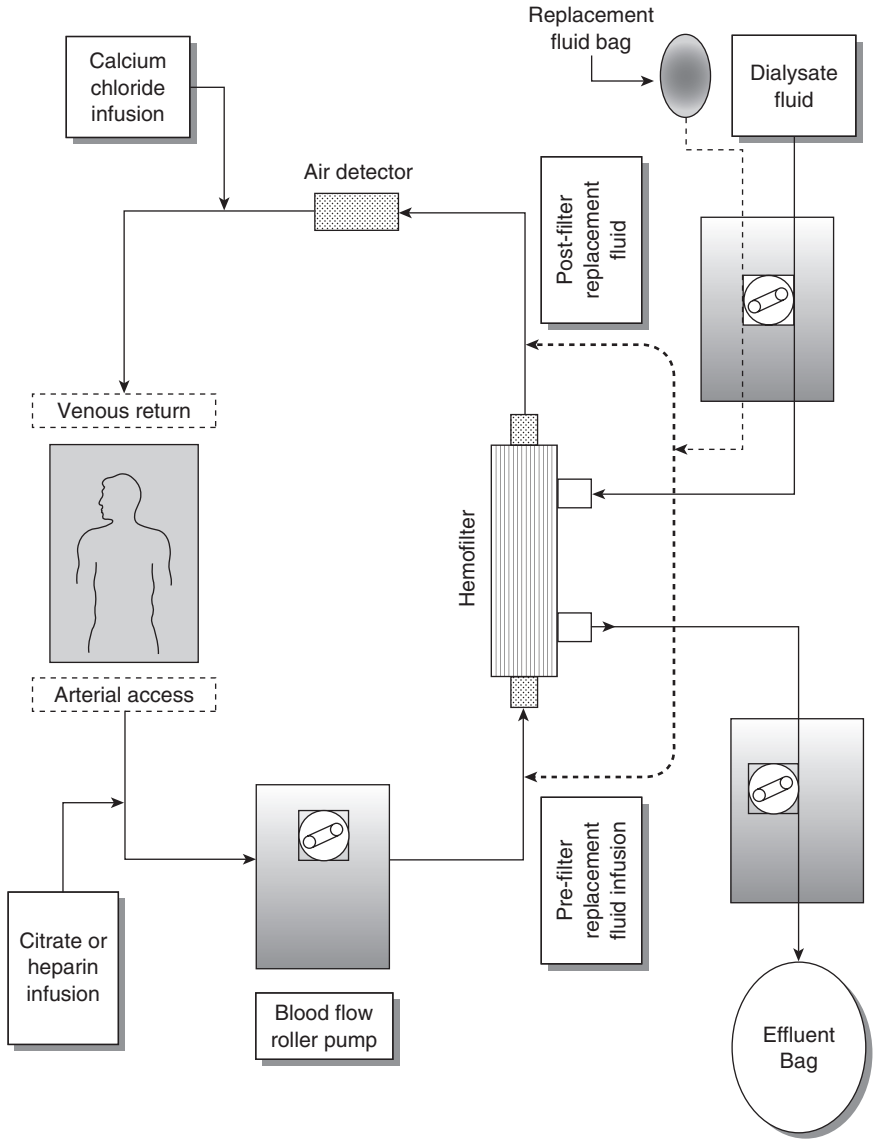

Figure 27.4 Mechanics of CRRT machines (continuous venovenous modality). Blood is pumped from the patient via the 'arterial' catheter port, using a roller pump. Regional anticoagulation with either citrate or heparin, is achieved by prefilter infusion of the anticoagulant. Arrows indicate the direction of blood flow or fluid path in the CRRT circuit. Dotted lines indicate path for replacement fluid infusion in either the prefilter or postfilter location. Spent dialysate and ultrafiltrate and collected in the 'effluent bag', which is discarded.

However, Normocarb is not approved by the US Food and Drug Administration (FDA) for this purpose. Other commercially available CRRT dialysate solutions and their compositions are shown in Table 27.4. None of these solutions are, however, approved by the FDA for use as replacement solutions at the present time.

Anticoagulation

Anticoagulation is necessary for the CRRT circuit to remain clot-free and allow adequate dialyzer function. Commonly used anticoagulation regimens in CRRT include normal saline flushes, heparinization, and citrate anticoagulation.

Saline flushes

Flushing the extracorporeal lines, blood pump, the hemofilter, and air detectors with sterile normal saline can allow effective functioning of the CRRT procedure in a patient with bleeding diathesis, or when anticoagulation is contraindicated. In order to adopt this technique, a three-way stopcock is placed at the connection of the 'arterial' side of the CRRT circuit and the vascular access. When performing a normal saline flush, the blood flow in the CRRT circuit is decreased to 100 ml/min in order to prevent the formation of bubbles in the blood tubing. The three-way stopcock is then closed to the patient and opened to a bag of normal sterile saline. The saline (10–20 ml) is then flushed through the CRRT circuit at a flow rate of

Table 27.3 Recommended catheter sizes and insertion sites in infants and children

Patient size	Catheter size and location	Site of insertion
Neonate		
<3–5 kg	Two 5 French single-lumen	Femoral and internal jugular vein(s)
	Single 7 French double-lumen, 10 cm (Medcomp)	Internal jugular, femoral veins
	Single 7 French double-lumen, 13 cm (Cook)	Femoral vein
	Two 7 French umbilical vein lines	Umbilical veins
Infants/school-age		
5–15 kg	Single 7 French triple-lumen, 16 cm (Arrow)	Internal jugular, subclavian, or femoral veins
	Single 8 French double-lumen, 11–16 cm (Arrow)	
	Single 9 French double-lumen, 12–15 cm (Medcomp)	
10–20 kg	Single 9 French double-lumen, 12–15 cm (Medcomp)	
	Single 10 French double-lumen, 12–19.5 cm (Mahurkar)	
	Single 11.5 French double-lumen, 12–20 cm (Medcomp, Mahurkar)	
	Single 11.5 or 12 French triple-lumen, 12–20 cm (Medcomp, Mahurkar, respectively)	
Pediatric		
>20 kg, but <70 kg	Single 11.5 French double-lumen, 12–20 cm (Medcomp, Mahurkar)	Internal jugular, subclavian, or femoral veins
	Single 11.5 or 12 French triple-lumen, 12–20 cm (Medcomp, Mahurkar, respectively)	
Adolescent		
>70 kg	Single 11.5 French double-lumen, 12–20 cm (Medcomp, Mahurkar)	Internal jugular, subclavian, or femoral veins
	Single 12 French double-lumen, 15–20 cm (Cook)	
	Single 11.5 or 12 French triple-lumen, 12–20 cm (Medcomp, Mahurkar, respectively)	

100 ml/min. The inner lumen of the tubing and filter fibers are visually inspected during the procedure for evidence of any clot formation. The volume of normal sterile saline infused during the flush must be recorded as IV fluid administered to the patient.

Heparin

Heparin has long been the mainstay of anticoagulation in CRRT. Typically, the CRRT circuit is primed with 1–2 L of normal sterile saline containing 2500–5000 units/L of heparin. Then, a prefilter heparin infusion is initiated, with a heparin bolus of 10–20 units/kg if the initial ACT is < 160 seconds followed by a continuous infatuation at 5–10 units/kg/h with a goal activated clotting time (ACT) of 180–220 seconds. The ACT or activated partial thromboplastin time (aPTT) is used to monitor the adequacy of the heparinization. ACT is commonly performed at the bedside, decreasing the turnaround time from the laboratory. Heparin dose is highly variable and must be individualized.[23]

Although the goal of heparin administration is to achieve regional anticoagulation of the extracorporeal circuit, heparin is not removed by the CRRT process itself and leads to systemic heparinization of the patient. Consequently, heparin-associated bleeding has been reported to occur in as many as 50% of patients receiving CRRT, especially in patients at risk for such a bleeding.[23] Heparin use can also result in heparin-induced thrombocytopenia (HIT) in 1–5% of patients due to development of antiplatelet factor 4/heparin (PF4/H) antibodies.[24]

Citrate anticoagulation

In 1990, Mehta et al demonstrated the efficacy of citrate anticoagulation for CRRT circuits.[25] Citrate anticoagulation is based upon the concept of chelation of the calcium in order to avoid clotting of blood in the CRRT circuit. Calcium is necessary for the activation of factors XI, IX, X, and prothrombin. Thus, chelation of free calcium by citrate inhibits the activation of the intrinsic pathway of coagulation, thereby resulting in anticoagulation.

By infusing citrate in the prefilter position, truly regional anticoagulation of the hemofilter, without systemic anticoagulation of the patient, can be achieved. However, intravenous calcium

Table 27.4 Commercially available bicarbonate-based, FDA-approved CRRT dialysate solutions

			Prismasate						Duosol			Accusol			
	Plasma	Normocarb	BK 0/3.5	BGK 2/0	BGK 4/0	BGK 4/2.5	B25GK 4/0	BK 2/0	#4450	#4551	#4552	5B9250	5B9249	5B9248	5B9251
Na^+ (mmol/L)	135–145	140	140	140	140	140	140	140	136	140	140	140	140	140	140
K^+ (mmol/L)	3.5–5.0	0	0	2	4	4	4	2	2	0	2	0	2	4	2
Cl^- (mmol/L)	100–108	106.5	109.5	108	110.5	113	120.5	108	107	109	111	109.5	111.5	113.5	116.3
Lactate (mmol/L)	0.05–2.0	0	3	3	3	3	3	3	0	0	0	0	0	0	0
HCO_3^- (mmol/L)	22–26	35	32	32	32	32	22	32	25	35	35	35	35	35	30
Glucose (mg/dL)	70–110	0	0	110	110	110	110	0	0	100	100	0	100	100	100
Ca^{2+} (mmol/L)	2.3–2.6	0	3.5	0	0	2.5	0	0	0	3	3	3.5	3.5	3.5	2.8
Mg^{2+} (mmol/L)	1.4–2.0	1.5	1.0	1.0	1.5	1.5	1.5	1.0	1.5	1	1	1	1	1	1.5
Osmolality	280–296		287	292	296	300	296	286							
Volume (L)		3.24	5	5	5	5	5	5	5	5	5	2.5	2.5	2.5	2.5

Normocarb, Dialysis Solutions, Inc., Richmond Hill, Ontario; Prismasate, Gambro Renal Products, Inc., Lakewood, Colorado; Duosol, B. Braun, Melsungen, Germany; and Accusol, Baxter Healthcare, Inc., Deerfield, Illinois.

infusion needs to be provided in the systemic circulation of the patient in order to correct hypocalcemia induced by citrate infusion in the extracorporeal circuit. Citrate is cleared by CRRT, with its clearance reported to equal that of urea clearance in CRRT in both diffusive and convective modalities.[26]

Bunchman and colleagues have adopted citrate infusion protocols designed for use in pediatric patients.[21,22] They administered ACD-A solution (Baxter Healthcare, Inc., Deerfield, Illinois) in prefilter location through a three-way stopcock placed at the connection between the arterial bloodline and the vascular access. The ACD-A infusion (in ml/h) is initiated at 1.5× the blood flow rate (ml/min) in the CRRT circuit. Calcium chloride (8000 mg calcium chloride/l of normal sterile saline, or 8 mg/ml) infusion is begun through either a third lumen of a triple-lumen dialysis catheter, or through a different central venous line at 0.4× the ACD-A infusion rate in ml/hr.[21,22] The circuit ionized calcium (iCa) is checked postfilter (post-ACD-A infusion) with a target iCa^{2+} of 0.35–0.50 mmol/l. The systemic ionized calcium is checked either through a central line or pre-ACD-A site in the arterial limb of the CRRT circuit, with a target iCa^{2+} of 1.1–1.3 mmol/L.[21,22] The ACD-A and calcium chloride infusions are titrated per guidelines given in Tables 27.5 and 27.6.

Complications of citrate anticoagulation include hypocalcemia, metabolic alkalosis, and citrate toxicity. Hypocalcemia is avoidable by following titration guidelines for infusion of the calcium chloride. Metabolic alkalosis develops due to hepatic conversion of 1 mole of citrate to 3 moles of bicarbonate. ln the authors' experience, all children treated with ACD-A citrate anticoagulation developed metabolic alkalosis.[21,22] Indeed, failure to develop a metabolic alkalosis while receiving citrate anticoagulation should lead to the search for an underlying metabolic acidosis and a mixed acid–base disorder in the patient. The metabolic alkalosis is treated by decreasing the dialysate flow (in CVVHD mode) by approximately 30%, and by substituting replacement fluid with sterile saline at a flow rate approximately 30% of the previous total dialysate flow rate, so that the combined dialysate and replacement fluid rates are 2000 mL/hour/1.73 m^2.[2]

Citrate toxicity may be diagnosed by monitoring the ratio of the total-to-ionized calcium ratio (systemic-to-CRRT ionized calcium).[27] A total-to-ionized calcium ratio of >2.5 represents citrate toxicity.[27] Whereas the overall prevalence of citrate toxicity was 12% in this single-center experience, it affected 33% of patients with ARF complicating hepatic failure.[27]

Apart from less bleeding complications compared with heparin use, citrate anticoagulation may also offer increased survival of the CRRT circuit. A recent study found that the citrate-anticoagulated circuits lasted a median of 70 hours, compared with a median of 40 hours for heparin-anticoagulated circuits.[28] The rate of spontaneous circuit failure was 87% in the heparin arm, and 57% in the citrate arm.[28] In contrast, in a multicenter prospective, non-interventional study, mean circuit life was similar between heparin- and citrate-anticoagulated systems (42.1 ± 27.1 vs 44.7 ± 35.9 hours, respectively).[29]

Complications

Complications of CRRT result from technical issues such as vascular access and device malfunction and failure as well as those that may result from clinical impacts of the procedure itself (Table 27.7).[30]

Table 27.5 Adjustment of citrate infusion by circuit ionized calcium

CRRT circuit iCa^{2+} (mmol/L)	Weight >20 kg Action	Weight <20 kg Action
<0.35	↓rate by 10 ml/h	↓rate by 5 ml/h
0.35–0.40	No change	No change
0.41–0.50	↑rate by 10 mL/h	↑rate by 5 ml/h
>0.50	↑rate by 20 ml/h	↑rate by 10 ml/h

Titrate citrate (ACD-A) drip in order to maintain CRRT circuit iCa^{2+} between 0.35 and 0.40 mmol/L. Physician review of therapy is indicated if ACD-A infusion rate is >200 ml/h.

Table 27.6 Adjustment of calcium chloride infusion by patient's peripheral ionized calcium

Patient iCa^{2+} (mmol/L)	Weight >20 kg Action	Weight <20 kg Action
>1.30	↓rate by 10 ml/h	↓rate by 5 ml/h
1.10–1.30	No change	No change
0.90–1.10	↑rate by 10 ml/h	↑rate by 5 ml/h
<0.90	↑rate by 20 ml/h	↑rate by 10 ml/h

Titrate calcium chloride drip rate in order to maintain the patient's iCa^{2+} between 1.10 and 1.30 mmol/L.

Table 27.7 Complications of CRRT

Technical failings	Clinical events
Vascular access failure	Bleeding
Circuit clotting	Infection (catheter-related and bacteremia)
Occlusion of catheter	Hypothermia
Inadequate blood flow for clearance	Nutritional losses
Tubing malfunction/separation	Hypotension
Air embolism	Electrolyte disturbance
Loss of clearance over time	

Technical and equipment malfunction

Complications associated with the vascular catheter itself, such as kinking, partial or complete obstruction, or displacement, can lead to malfunction or cessation of the CRRT.[30] Device (or machine) can experience failure of the integrity of the tubing set; air may enter into the blood tubing and result in air embolism.[30] Newer CRRT devices are equipped with air detectors that clamp the blood return line to the patient if air is detected within the tubing set. Errors of ultrafiltration are uncommon with modern CRRT equipment, unless the device controls are intentionally overridden by the operators manually. Finally, the efficiency of clearance of the hemofilter may deteriorate due to the accumulation of blood proteins and blood cells along the intravascular side of the capillary filters.[30]

Bleeding

Anticoagulation-associated bleeding is a well-known complication seen in CRRT. The source of bleeding is often at the catheter exit site, but can also be internal at the vascular puncture site. Because of systemic heparinization, internal bleeding – such as in the gastrointestinal tract and other vital organs – can be severe.

Infection

The risk of infection from placement of the AV access can add significantly to the morbidity in a critically sick patient. In suspected sepsis, blood should be cultured from the peripheral source as well as from the dialysis catheter in order to distinguish catheter colonization from a bacteremic state.

Hypotension

Despite the slow nature of CRRT, hypotension due to excessive ultrafiltration of the intravascular space can result in hypertension.

Electrolyte disturbances

Hypokalemia and hypophosphatemia can occur if dialysate or replacement fluid has not been appropriately reconstituted. This is particularly important when using CRRT for intoxications or inborn errors of metabolism. Often these children do not have ARF, and thus the potassium restriction and phosphorus restriction during CRRT may result in significant hypokalemia and/or hypophosphatemia.

With use of citrate anticoagulation, dextrose in the citrate infusion (ACD-A solution) may deliver significant amounts of glucose, enhancing the risk of hyperglycemia in the patient. Similarly, hyperglycemia can develop with the use of peritoneal dialysis solutions as dialysate in CRRT.[31,32]

Hypothermia

Extracorporeal circuits can have a cooling effect upon the patient, and cooling towards room temperature is common. This is especially likely if the CRRT device lacks blood-warming capability. As pointed out above, extracorporeal cooling of blood may mask development of clinical fever in the critically sick patient.

Nutritional losses

Malnutrition often accompanies ARF as a result of hypercatabolism. An increased mortality and morbidity, as well as an increased length of hospital stay as a result of malnutrition, has been well established in adults.[33] Given these risks in the ARF, the goal should be to maximize nutrition and to reverse the catabolic state in these patients. Optimal nutritional management of ARF in adults includes increasing the protein content while possibly providing lower total caloric intake.[34,35] In adult patients with ARF requiring CVVH, provision of ≥ 1 g/kg/day of protein has been associated with a trend towards a higher normalized protein catabolic rate (nPCR), and a smaller nitrogen deficit, as compared to those patients with an intake of < 1 g/kg/day protein.[34] However, even with CRRT therapy, it is often difficult to get a catabolic patient with ARF into a positive nitrogen balance.[36]

Significant dialytic clearance of amino acids has been noted during CRRT, especially with addition of dialysis. Loss of amino acids can range from 1.5 to $> 100\%$ of certain amino acids, with higher dialytic clearance associated with the higher ultrafiltration rate.[37] Maxvold et al compared amino acid loss and nitrogen balance in critically ill pediatric patients requiring CVVH and CVVHD who were receiving similar dialysate or replacement fluid rates and total parenteral nutrition.[38] They noted that amino acid loss was greater with CVVH than with CVVHD, and these losses accounted for approximately 12% and 11% of the total daily protein intake, respectively.[38] It has been suggested that amino acid intake should be enhanced by around 12 g/1.73 m^2/day above the standard recommendation of 1.5 g/kg/day of amino acids (protein) in pediatric patients undergoing CRRT.[38]

Micronutrients are also removed by both diffusive and convective CRRT. A negative net balance of selenium, copper, and thiamine while having a slightly positive net balance of zinc has been shown to occur with hemodiafiltration.[39] Trace element supplementation with selenium, and possibly other micronutrients, may be necessary in situations of prolonged CRRT.

CRRT in neonates

The use of CRRT in the neonatal patient requires a close attention to the potential for adverse events. Due to the small intravascular blood volume of neonates, careful attention must be paid to their volume status and the percent of intravascular blood volume to be contained in the extracorporeal circuit.

Blood flow rate

The blood flow rate in the neonatal and young infant is targeted at 5–10 ml/kg/min. However, this may lead to too slow blood flow through the extracorporeal CRRT circuit, and result in clotting of the CRRT circuit, and the need for its frequent replacement. In order to overcome these problems, our recommendation is to run the CRRT blood flow at a minimum speed of 50 ml/min in neonates, irrespective of body weight.

Blood priming

If the calculated extracorporeal blood volume of the CRRT circuit exceeds 10% of the patient's estimated intravascular blood volume in neonates and infants, then the CRRT circuit should be primed with whole blood in order to prevent acute volume depletion and hypotension. Priming the circuit with normal saline or 5% albumin should be avoided because of the risk of hemodilution of the patient's hematocrit.

Serious life-threatening hyperkalemia, metabolic acidosis, and hypotension have been reported with priming of the CRRT circuits with stored unbuffered blood.[40,41] These manifestations are believed to be a specific bioincompatibility with AN69 membrane hemofilters (Prisma) that results in activation of leukocytes and release of bradykinin when stored acidemic blood comes in contact with this membrane.[40]

A 'bypass maneuver' in order to minimize the chances of the complication described above has been suggested. In this procedure, the patient's blood, after its 'first pass' through the hemofilter is discarded, while simultaneously providing a blood transfusion of packed red blood cells diluted with normal saline in a ratio of 1:1. The procedure requires placement of two three-way stopcocks on the venous return line of the extracorporeal circuit.[40] The patient's blood containing any activated leukocytes after contact with the hemofilter membrane is drained into a waste bag connected to the proximal three-way stopcock. Blood is transfused to the patient via the distal three-way stopcock. During the procedure, the CRRT device blood pump is set to a flow rate of 10 ml/min, and the packed red blood cell solution is infused at 600–900 ml/h (10–15 ml/min).[40] Buffering of the packed red blood cells in order to normalize the pH and neutralize the citrate content in order to minimize or prevent bradykinin release has been recommended (Table 27.8).[40]

Predialysis of the blood prime of a CRRT circuit for use in neonates has been reported, resulting in the near-physiologic correction of the metabolic acidosis and hyperkalemia commonly seen in banked blood. The procedure is instituted by recirculation and zero-balance ultrafiltration hemodialysis of the blood prime, prior to connecting the patient to the CRRT circuit.[42] Zero-balance ultrafiltration (Z-BUF), another technique of correcting the hyperkalemic, hypercitratemia, and metabolic acidosis of the priming blood uses recirculation of the blood after buffering it with 5% albumin in a ratio of 60/40 and performing zero ultrification continuous hemofiltration for 30 minutes prior to the initiation of CRRT.[43] Dialysate flow rate in the Z-BUF technique prime predialysis is recommended at 2 L/h and the procedure is conducted for 30 minutes.[43] With this technique, these authors found nearly normalized blood pH and serum electrolytes, while having virtually no effect on the tumor necrosis α (TNFα) and interleukin IL-1β and IL-6 levels pre- and post-Z-BUF.[43] However, a significant reduction in bradykinin in the blood prime was noted.[43]

Table 27.8 Composition of the modified blood prime for AN69 filter

Component	Amount
Packed red blood cells	300 ml
Tris-hydroxy-methyl aminomethane (THAM)	50 ml
Calcium chloride (27%)	250 mg
Heparin (100 units/ml)	5–7 ml (500–700 units)
Mix equal parts with:	
Sterile water	850 ml
Sodium bicarbonate (1 mEq/ml)	150 ml

Reproduced with permission from Brophy et al.[40]

Outcome

An overall survival rate of 38%, with a survival rate of 25% in those children weighing less than 3 kg and of 41% in those weighing between 3 and 10 kg has been reported recently.[44] Mean blood flow rate in this series was 9.5 ± 4.2 ml/kg/min, and mean duration of CRRT was 7.6 ± 8.6 days.[44] Survivors weighing more than 3 kg required fewer vasopressor medications than non-survivors, and there was no difference in outcome based upon the use of convective or diffusive clearance.[44] The clinical conditions in these patients were congenital heart diseases (16.5%), metabolic disorders (16.5%), MODS (15.3%), sepsis (14.1%), and liver failure (10.6%).[44]

CRRT in extracorporeal membrane oxygenation

Technically, the merging of CRRT and ECMO requires an appreciation of the effect of shunting blood flow from the membrane oxygenator to the hemofilter. CRRT may be accomplished by use of either a dedicated CRRT machine (CVVHD) or the insertion of a postpump hemofilter (Figure 27.5).

CAVH module

A more simple form of CRRT on an ECMO circuit consists of a CAVHD arrangement, using the ECMO pump itself to drive the extracorporeal circulation of blood through the CRRT hemofilter. In this arrangement, the arterial line is placed postpump, either preoxygenator or postoxygenator position, with

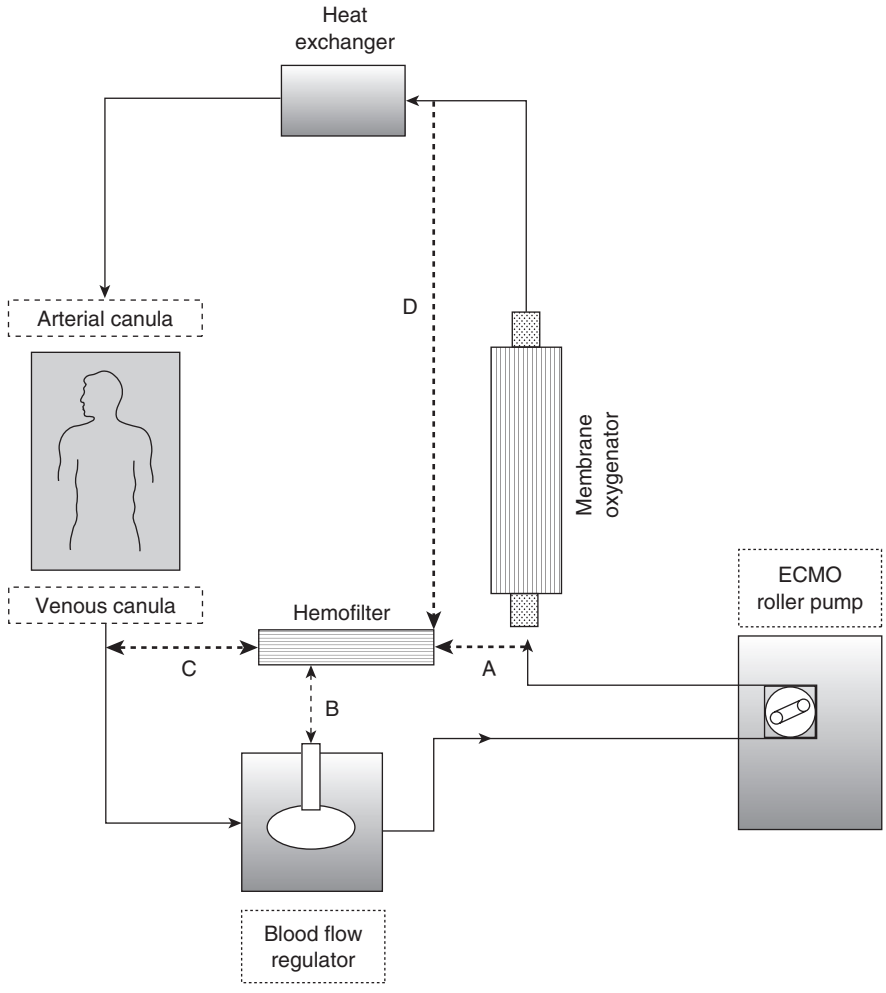

Figure 27.5 CRRT circuit configuration in ECMO circuit. Dotted lines indicate possible sites of arterial and venous connections for the CRRT circuit. Arrowheads indicate direction of blood flow. Bidirectional arrows indicate that either the 'arterial' or 'venous' connection can be established at this port. Arterial access placed post-ECMO pump but pre-ECMO oxygenator (A) is the best-suited orientation for the 'arterial' line of a hemofilter in a CAVH arrangement. The 'venous' return line can return the blood either directly into the bladder (B), or into the pre-bladder segment (C). When using a dedicated CRRT machine, the 'arterial' line should be placed in the low pressure side of the ECMO circuit (i.e., before the ECMO pump). In this orientation, arterial access can be established either from the bladder (B) or from the pre-bladder segment (C), with the venous return going into either the pre-bladder segment (C) or into the bladder (B), respectively. While post-ECMO oxygenator (D) 'arterial' connection is also possible, high CRRT pressure in the circuit may shorten circuit life and interfere in the functioning of the ECMO circuit itself. To lessen the risk of air embolization, 'venous' connection should always be in either pre-ECMO bladder (C) or directly into the bladder (B).

the venous return line returning to the bladder (see Figure 27.5, arterial lines A or D, returning from hemofilter through path B).

The main concern in this procedure is uncontrolled diversion of blood to the hemofilter, resulting in a 'steal' phenomenon from the ECMO circuit. Quantification of the 'steal' phenomenon can be measured by the difference in ECMO blood flow necessary to maintain the mixed central venous SvO_2 at the same level prior to and immediately after diverting blood flow to the hemofilter.[45] Calculating the hemofilter blood flow in this arrangement of CRRT on an ECMO circuit can be carried out using the following formula:

$$\text{Patient blood flow \%} = \frac{[CaO_2 - (\text{postoxygenator}) - CvO_2 - (\text{preoxygenator})]}{[CaO_2 - (\text{postoxygenator}) - CvO_2\ (\text{prebladder})]} \times 100$$

$$\text{Hemofilter (CRRT) blood flow \%} = 100 - \text{Patient blood flow \%}$$

Dedicated CRRT device

A diagrammatic representation of connecting a dedicated CRRT machine in an ECMO circuit is shown in Figure 27.5. In infants and small children, the blood flow of an ECMO circuit may not result in a 'steal' phenomenon from the CRRT bloodlines in their orientation. However, with high blood flow of the ECMO in children and adolescents, this 'steal' phenomenon can become more evident, leading to less blood flow into the arterial side of the CRRT circuit. The 'steal' phenomenon causes an increase in the 'arterial' (access) pressure (a more negative pressure reading) and alarms will be triggered in the CRRT device. Similarly, if the venous line of the CRRT device is placed in the postpump position of the ECMO circuit, the high blood flow may overcome the venous pressure in the CRRT circuit and result in the backflow of blood into the CRRT

circuit and cause venous pressure alarms (a too positive pressure reading) in the CRRT device. Therefore, it is important to place both the 'arterial' and 'venous' lines of the CRRT circuit in the low-flow sections of the ECMO circuit. Because of the above considerations, the preferred locations for placement of the CRRT access lines are to have the arterial access withdrawing from the bladder and the venous line returning to the prebladder position (withdrawn at B and return to C) or to have the arterial access withdrawing from the prebladder position and the venous line returning directly into the bladder (withdrawn at C and return to B, see Figure 27.5).

Outcome

Outcome of CRRT on ECMO is dependent more upon the underlying disorder requiring treatment with ECMO than with the ARF requiring CRRT. In one study, 6 of 27 patients receiving ECMO therapy developed ARF and need for CRRT. Of these patients, only 2 patients survived.[46] Another retrospective study of 35 pediatric patients less than 18 years of age receiving CRRT with ECMO therapy found an overall survival of 43%, with 93% of survivors recovering their renal function.[47] This latter study also found that the use of vasopressors on ECMO and CRRT portended a poor outcome for patients.[47]

CRRT in inborn errors of metabolism

CRRT has been used effectively to correct metabolic derangements associated with a variety of inborn errors of metabolism. Children with a suspected or confirmed inborn error of metabolism often require an extracorporeal therapy in order to achieve a rapid correction of their metabolic disturbance.

Accumulation of ammonia is the primary abnormality encountered in urea cycle disorders. In these patients, CRRT modalities can achieve an excellent clearance of ammonia and rapid correction of the hyperammonemic coma.[48–56] The extracorporeal clearance of ammonia with CRRT must always be accompanied by the use of alternative pathway medications for the removal of nitrogen.

Branched-chain amino acidemias, such as maple syrup urine disease, methylmalonic acidemia, propionic acidemia, and isovaleric acidemia, have been successfully treated using CRRT.[52] As in urea cycle disorders, CRRT provides rapid and ongoing removal of accumulated branched-chain amino acids and their ketoacid metabolites that are responsible for the neurologic sequelae of these disorders.

CRRT in multi-organ dysfunction syndrome

MODS is defined as a clinical condition characterized by simultaneous failure of two or more organ systems.[57,58] A recent report by the Prospective Pediatric CRRT (ppCRRT) Registry Group described MODS as the indication in 181 of 294 pediatric patients who received CRRT.[59] In this cohort, sepsis (28.7%) and cardiovascular shock (16.0%) were the most common causes of MODS. Overall patient survival from MODS requiring CRRT support was 50.8%.[59] Mean percent fluid overload at the time of intensive care unit (ICU) admission and the PRISM2 score at the time of initiation of CRRT had a significant impact on patient survival.[59] Survival rates were better for patients having < 20% fluid overload (survival 61%) at the time of initiation of CRRT than for those patients with > 20% fluid overload (survival 32%).[59] These data support the concept of goal-directed fluid therapy and that of early initiation of CRRT in the treatment of MODS.

CRRT in malignancy

CRRT has been used to prevent life-threatening electrolyte, fluid overload, or acid–base disturbances in patients with malignancies, or following hematopoietic cell transplantation. In tumor lysis syndrome, the destruction of the large tumor or white blood cell burden by chemotherapeutic agents results in hyperuricemia, hyperkalemia, and hyperphosphatemia with associated hypocalcemia. Use of both CAVH and CVVH has been demonstrated to normalize serum uric acid, potassium, and phosphorus levels in children at risk for development of tumor lysis syndrome.[60,61]

Another significant oncologic population at risk for ARF is the hematopoietic cell transplant recipient. Incidence of ARF in these patients, defined as a doubling of the serum creatinine, is 25–50% of the population.[62] The ppCRRT Registry Group recently reported on the outcomes of 44 pediatric patients (status – post bone marrow transplantation) who required CRRT.[63] Overall patient survival to ICU discharge was 40%, with a trend towards improved survival from 2003 to 2004 in the ppCRRT Registry (36% and 44%, respectively). In this retrospective cohort study, mean airway pressure at the termination of CRRT was significantly greater (26.06 ± 2.02 vs 8.44 ± 2.69 mmHg) in the non-survivors than the survivors. In this analysis, the percent of fluid overload did not discriminate between survivors and non-survivors.

Finally, the role of CRRT in the management of bone marrow transplant recipients has been further examined for its effects on those patients who develop acute respiratory distress syndrome (ARDS). In an uncontrolled, non-randomized case series, DiCarlo et al initiated CRRT concomitantly with intubation for ARDS in 6 pediatric bone marrow transplant recipients, 3 patients following chemotherapy, and 1 patient with lymphoma/hemophagocytosis.[64] These authors achieved a very high rate of clearance of 50 ml/min/1.73 m^2 by performing hemofiltration with a replacement solution at 1800 ml/h and dialysis with a countercurrent dialysate solution at 1800 ml/h.[64] Eighty percent of these patients survived to hospital discharge with recovery of their native renal function.[64] Thus, early and aggressive use of CRRT in order to normalize

fluid balance and potentially high clearance rates may contribute to an improved survival in those hematopoietic cell transplant recipients who develop either ARF, volume overload, or ARDS.

CRRT in hyperosmolality

Hyperosmolar disorders due to hypernatremia have previously been associated with a mortality rate of up to 70% in pediatric patients.[65,66] Two recent reports describe the slow correction of hyperosmolality using CRRT and hypertonic dialysate or replacement fluid.[65,66]

CRRT in intoxications and poisoning

The ability of an extracorporeal therapy to remove an intoxicant is affected by the volume of distribution of the drug. Generally, drugs with volumes of distribution of < 1 L/kg (total body water) are amenable to dialytic removal.[67] Drugs with large volumes of distribution are less likely to be effectively removed by dialysis, and are more likely to result in rebound elevations of blood levels following a dialytic therapy. Large molecular weight drugs are more difficult to dialyze than low molecular weight drugs. High-efficiency dialysis filters can overcome this size barrier to some extent. The degree of protein binding has a negative effect upon a drug's dialyzability. However, if protein-binding sites are fully saturated, free drug may be amenable to dialytic clearance.

Numerous medications have been described as being cleared by CRRT. Although a complete list is beyond the scope of this chapter, some medications reported to be removed include vancomycin, lithium, ethylene glycol, procainamide, theophylline, methotrexate, phenytoin, carbamazepine, and valproic acid.[68–77]

Use of albumin dialysis has been reported to aid in the removal of highly protein-bound drugs. Askenazi et al described the use of albumin-dialysis using CVVHD to treat an acute, severe carbamazepine overdose.[77] These authors found a dramatic decrease in the serum half-life of carbamazepine (from 25–60 hours to 7–8 hours) using albumin dialysis CVVHD.[77] Phenytoin and valproic acid removal have been reported to be enhanced with albumin dialysis compared to standard high-efficiency CVVHD.[76,78]

Combined CRRT and plasmapheresis

The combination of plasmapheresis and CRRT may be occasionally performed in the management of immune-mediated diseases complicated by ARF. In most instances, however, the CRRT treatment is discontinued during the plasmapheresis, and resumed after the completion of the plasmapheresis. Stopping CRRT may cause citrate accumulation during plasmapheresis, lead to hypocalcemia, and poses a risk for hemodynamic instability.[79]

Yorgin et al described the use of concurrent plasmapheresis and CRRT in the treatment of a 14-year-old female with leukemia.[80] In this instance, the authors placed a three-way stopcock at both the arterial and venous sides of the double-lumen dialysis catheter.[80] The three-way stopcocks allowed for parallel flow of the arterial blood through both the centrifugation plasmapheresis circuit and the CRRT circuit, and parallel return venous blood flow back to the patient. Alternately, in an in-series configuration, plasmapheresis circuit withdraws the patient's blood from the arterial side of the double-lumen catheter, and the venous return line of the plasmapheresis circuit is then connected in-series to the arterial line of the CRRT circuit. The blood from the venous return line of the CRRT circuit is eventually returned to the patient through the venous return side of the double-lumen dialysis catheter. Using this technique, citrate anticoagulation of the plasmapheresis circuit can then undergo high dialytic clearance.[81]

Outcome

Experience in using concurrent centrifugation plasmapheresis and CRRT is limited. Ponikvar et al have reported its use on 21 neonates and infants.[82] These authors found that recovery of renal function occurred in 47.6% of patients, with an overall patient survival of 42.9%.[82] Complications of concurrent therapy include hemofilter thrombosis, catheter malfunction, hypotension and bradycardia, and pulmonary edema.[82]

Single-pass albumin dialysis

A new use of CRRT circuits is that of single-pass albumin dialysis (SPAD) for the dialytic clearance of protein-bound inflammatory mediators or toxins. The molecular adsorbents recirculation system (MARS), in phase I clinical trials, was found to decrease plasma ammonia and total bilirubin levels, increase the Fischer ratio (the ratio of branched-chain amino acids to aromatic amino acids) and factor VII levels, and to decrease hepatic encephalopathy and intracranial pressures.[83] Of 5 patients listed for hepatic transplant as UNOS (United Network for Organ Sharing) status 1, 1 patient had recovery of native liver function and 3 patients were bridged using the MARS to hepatic transplantation.[83]

Due to the complexity and cost of the MARS circuit, efforts to adapt current CRRT machines to perform SPAD have been undertaken. Although the basic concepts of SPAD are the same as MARS, in SPAD there is no regeneration of the albumin dialysate, resulting in a single pass of the albumin dialysate with subsequent discarding of it in the effluent bag.

In-vivo use of SPAD has been reported in case reports and case series to treat acute hepatic failure in Wilson disease and acute hepatitis with hyperbilirubinemia.[84–86] Kreymann et al prepared a 44 g/L (4.4%) albumin dialysate by replacing 1 L of a

4.5 L bicarbonate-based dialysate with 20% albumin.[84] CRRT was performed as CVVHDF, without apparent modification from the standard protocol. These authors found significant albumin dialysis clearance of copper and total bilirubin, with a resultant improvement in the patient's hepatic encephalopathy and electroencephalography (EEG).[84] Harvey et al reported on the use of SPAD in an adolescent female with acute fulminant hepatic failure due to Wilson disease who was bridged to successful orthotopic liver transplantation.[85] These authors prepared the albumin dialysate using 5% albumin added to a bicarbonate-based dialysate, and ran the dialysate at 1–2 L/h of flow. This patient experienced a reduction in her transfusion requirements, serum copper concentrations, and conjugated bilirubin, and improvements in her renal function and hepatic encephalopathy.[85] SPAD has been used to treat symptomatic hyperbilirubinemia in an adult with acute hepatitis.[86] Chawla et al compared bilirubin clearance using both 1.85% and 5.0% albumin dialysate, and found improved total bilirubin clearance using the 5.0% albumin concentration.[86] It appears that a 5% (50 g/L) albumin concentration would provide the best clearance when using SPAD. Specific cautions in the use of SPAD include the potential for hypernatremia. Methods to prevent a hypernatremic albumin dialysate include the reduction of sodium chloride in a pharmacy-made custom solution in order to offset the additional sodium content of the 25% albumin, or the use of a low-sodium 25% albumin preparation.

CRRT survival

Previous single-center reports of outcome following CRRT in pediatric patients found a survival rate of only 42%, ranging from 0% for bone marrow transplant recipients to 100% for tumor lysis syndrome.[87]

In a retrospective study, Goldstein and colleagues reported results in 21 pediatric patients receiving CVVH therapy, taking into account the patient's severity of illness by using the Pediatric Risk of Mortality 2 (PRISM2) score.[88] These authors identified the percentage of fluid overload as a significant predictor of mortality after controlling for severity of illness.[88] The ppCRRT has been established to collect retrospective data on CRRT in pediatric patients at 12 pediatric institutions across the United States. Reporting on 273 pediatric patients, the ppCRRT found an overall survival rate of 58%. Patients with hepatic failure or a hepatic transplant have the lowest survival rate (37%) and those with drug intoxication have the highest survival rate (100%).[89] Table 27.9 lists the survival by primary disease diagnosis, as well as by indication for CRRT.

Concluding remarks

Continuous renal replacement therapy has evolved over the past 30 years as an efficient and safe treatment for ARF in both adult and pediatric patients. New dialysate and replacement fluid solutions are available, and now we can safely use bicarbonate as the buffer in order to minimize cardiovascular instability and minimize the possibility of confounding the serum lactic acid levels. Anticoagulation for maintenance of the CRRT circuit is critical in providing adequate fluid and electrolyte therapy in the pediatric patient with ARF, and citrate anticoagulation appears to have multiple benefits over heparin anticoagulation. Vascular access is critical for proper functioning of a CRRT circuit, and ideally should use the largest catheter possible. Finally, CRRT may be a useful therapy in other clinical conditions, such as hyperosmolality, intoxications, hematopoietic cell transplantation, tumor lysis syndrome prevention, extracorporeal hepatic support, and plasmapheresis.

Table 27.9 Outcomes of CRRT by primary diagnosis

Primary diagnosis	Number	Survivors	Non-survivors	Percent survival
Sepsis	59	34	25	58
Bone marrow transplantation	43	19	24	44
Cardiac disease/transplantation	31	17	14	55
Malignancy (not tumor lysis syndrome)	24	13	11	54
Renal failure	20	14	6	70
Liver disease/transplantation	19	7	12	37
Hypovolemic shock	17	12	5	71
Inborn error of metabolism	16	9	7	56
Pulmonary disease/failure	12	7	5	58
Tumor lysis syndrome	11	9	2	82
Drug intoxication	9	9	0	100
Other	12	7	5	58
Overall	**273**	**157**	**116**	**58**

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28 Renal transplantation

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Renal transplantation is generally regarded as the treatment of choice for end-stage renal disease (ESRD) in children and adolescents. Although long-term dialysis therapy is possible, it is generally considered as a bridge to renal transplantation for pediatric patients with ESRD. Compared with chronic dialysis, renal transplantation offers survival advantage, improved linear growth, decreased hospitalization rate, and improved quality of life.[1–3] For these reasons, renal transplantation should be the goal for treatment of ESRD in childhood. Pre-emptive renal transplantation provides an opportunity for the child and the family to bypass dialysis altogether and remains a viable alternative for patients with a suitable donor.

Organ procurement, allocation, and data analysis

Organ procurement

The US Congress passed the National Organ Transplant Act in 1984 and established the Organ Procurement and Transplantation Network (OPTN) to facilitate and regulate organ transplantation in the United States. The United Network for Organ Sharing (UNOS), an independent non-profit organization, was established in 1984 and received a federal contract to operate OPTN in 1986.[4] UNOS is divided into 11 operational regions, and each region has a number of organ procurement organizations (OPOs) that are responsible for the procurement of organs from deceased donors and their shipment. OPTN, which is operated by UNOS, is responsible for allocation of deceased organs to all potential recipients in the United States.[5] This process is briefly described below.

Organ allocation

Listing on the UNOS 'waiting list'

After the evaluation and decision that the patient should receive a deceased organ renal transplant, the first step is to list potential recipients on the UNOS 'waiting-list'. The lay press and patients commonly refer to this list as the 'national list'. The qualifying criteria for a patient to be listed include being on dialysis, or having measured or estimated glomerular filtration rate (GFR) of less than 20 ml/min/1.73 m^2. Once listed, the potential recipient starts accumulating time on the 'waiting list'.

UNOS employs a point-based allocation policy developed through collaborative efforts between the transplant community, Scientific Renal Transplant Registry (SRTR), and OPTN.[4–6] The Donor allocation policy is based on scientific evidence to optimize outcomes in transplant recipients and is revised periodically as new data become available.

UNOS allocates organs based on a point system (Table 28.1). There is a mandatory sharing of 0 antigen-mismatched kidneys across the geographic and time zones in the United States. After fulfilling the above criteria, the procured kidneys are allocated

Table 28.1 UNOS point system for allocation of deceased donor kidneys

Factor	Points allocated	Condition
Time waiting	1 Fractions of 1	Each year of waiting time Prorated additional fraction of year
Quality of HLA match	Mandatory sharing 7 5 2	0 A, B, or DR mismatches 0 mismatch at B, DR loci 1 mismatch at B, DR loci 2 mismatches at B, DR loci
Panel reactive antibody	4	>80% with negative cross match
Pediatric recipient	4 3	Age <11 years Age 11–17 years
Organ donor	4	

in the following order: locally, then regionally, and finally nationally. Once an organ becomes available, donor information is entered in the UNOS computer system. The list of prospective blood group compatible recipients is generated based on their points. An offer is made to the first recipient deemed compatible by crossmatching. If that recipient is not compatible, the organ is offered to the next compatible recipient. Over the years, the organ allocation process has been refined. The recipients are allocated points, based on a number of factors. No points are assigned for 'medical urgency'.

Allocation of organs to pediatric recipients

Extra points are allocated to children in order to facilitate their renal transplantation. Children < 11 years of age get 4 extra points, and 3 points are allocated to children 11–17 years of age. In addition, pediatric renal transplantation goals have been established within UNOS to meet a predetermined time frame after patient listing on the 'waiting list'. The goal is to accomplish transplant within 6 months for children of 0–5 years of age, within 12 months for children of 6–10 years of age, and within 18 months for children of 11–17 years of age. If these goals are not met within the given time frame, these children are given priority on the list. UNOS is in the process of revising criteria for pediatric recipients.

Data analysis

A number of scientific registries maintain databases on ESRD and transplant outcomes.[1,2] These include UNOS, United States Renal Data System (USRDS), SRTR, and the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). All transplant centers are mandated to send information pertaining to all transplant recipients to UNOS following transplant and periodically. The SRTR collaborates with UNOS and plays a critical role in policy development through ongoing scientific analysis of data and development of statistical, analytic, and simulation models.

NAPRTCS, a consortium of pediatric ESRD and transplant centers, was established in 1987 with the scientific objectives of capturing information about current practice and trends in immunosuppressive therapy in children.[1] NAPRTCS has evolved as an important resource of information and ongoing research related to pediatric transplants performed in the United States, Canada, Mexico, and Puerto Rico. Participation in NAPRTCS is voluntary.

Immunologic barriers to transplantation

A number of immunologic barriers to successful transplantation exist, of which the most important ones are blood group antigens, human leukocyte (HLA) antigens, and pre-existing anti-HLA antibodies.[7]

Blood group

ABO compatibility between donor and recipient is an absolute prerequisite for successful transplantation.[7] ABO blood group antigens are expressed on the surface of endothelial cells, in addition to red blood cells (RBCs). Antibodies (naturally occurring isoagglutinins) to these antigens bind to the endothelium, cause hyperacute rejection (HAR) and irreversible graft loss. The rules that govern blood transfusion also apply to solid organ transplantation. Subjects with type O blood group are considered universal donors and those with type AB blood group are regarded as universal recipients. Experience in solid organ transplantation, including kidneys, across blood group barriers has begun to evolve in the past several years in some centers in the United States and Japan. In these experimental studies, blood group isoagglutinins are removed by plasmapheresis, or immunoadsorption, followed by intense immunosuppression.[8–10] Rh blood group antigen matching is traditionally not considered a requirement for successful renal transplantation.

Human leukocyte antigens

Genetic difference between individuals for the purpose of organ transplantation is recognized by differences in the composition of major histocompatibility complex (MHC) antigens, also known as HLA antigens.[11,12] The genes encoding these antigens are present on the short arm of chromosome 6. Based on their structural differences, HLA antigens are divided into class I (A, B, and C) and class II (DR, DQ, and DP). HLA class I antigens are present on all nucleated cells. RBCs lack HLA antigens. HLA class II antigens are present on macrophages, dendritic cells, endothelial cells, and B cells. T cells, renal tubular epithelial cells, and endothelial cells increase expression of class II molecules upon stimulation with cytokines such as γ-interferon (γ-IFN).

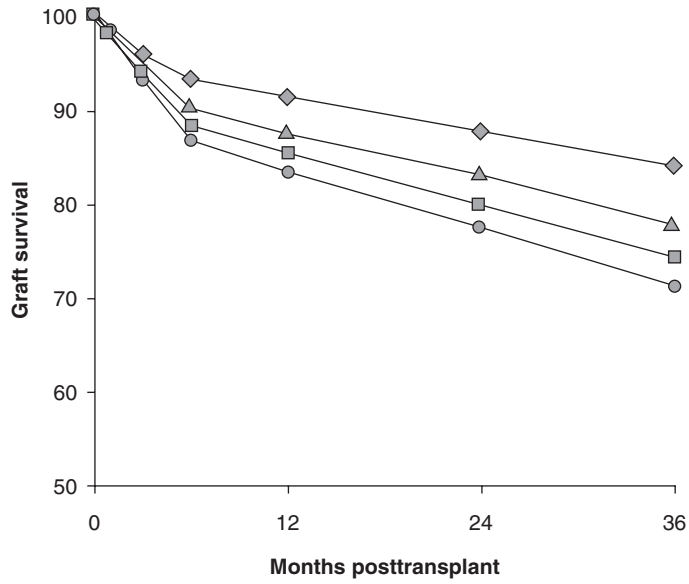
Histocompatibility genes are extremely polymorphic, and are expressed as co-dominant alleles. The concentration of HLA genes in one defined area of the chromosome allows these genes to be inherited as a packet, or haplotype. Individuals inherit 1 haplotype from each parent. Children are 1-haplotype matched with their biologic parents. Siblings can be complete HLA matched, 1-haplotype matched, or completely mismatched, depending upon the recombination of their haplotypes.

The HLA type of an individual can be determined either by conventional serologic methods, or by DNA-based typing.[11,13] Once the HLA typing is determined, the number of matched and mismatched antigens between the recipient and the prospective donor can be calculated. The number of mismatches, or non-shared HLA antigens between the donor and the recipient, may differ from the number of shared antigens or matches because of some non-typable HLA antigens, or because of inheritance of 2 copies of the same HLA allele. From the transplant perspective, only 6 antigens (A, B, and DR) are considered clinically important.

HLA mismatching determines the extent of anticipated allogenic response.[11] Availability of potent immunosuppressive

therapy has, to some extent, attenuated the effect of HLA matching on short-term allograft survival and the incidence of acute rejection (AR). However, HLA matching, in particular DR matching, continues to have an effect on long-term renal allograft survival.[14] HLA identical grafts have a longer half-life when compared to those that are less well matched. The half-life of the transplanted kidneys decreases in a step-wise fashion with increasing degree of HLA mismatching (Figure 28.1). The great degree of polymorphism makes complete HLA matching between two random individuals a rare event. Fewer than 20% of kidneys transplanted in the United States from deceased organ donors are completely matched for HLA antigens, or 0 mismatched.

The current clinical practice in the United States is to share all 6 antigen-matched, or 0-mismatched kidneys from deceased donors within the entire national recipient 'wait list' across geographic regions of the country.[3] The potential benefit of sharing 6 antigen-matched, or 0-mismatched kidneys in this manner may, however, be offset by the adverse effects of increased cold ischemia time associated with shipping the organs, sometimes over several time zones. Less than 6 antigen-matched kidneys are, generally, used locally.



HLA MM	n	T1/2
◇ 0	4750	14.7
△ 1–2	5659	11.7
□ 3–4	16 980	10.2
○ 5–6	9087	8.8

Figure 28.1 Effect of HLA mismatch on graft survival of unsensitized recipients reported to the UNOS in 1995–2001. HLA-matched recipients had a projected half-life of nearly 15 years compared with 9 years for those with 5–6 mismatches. (Reproduced with permission from Takemoto.[14])

Anti-HLA antibodies

Anti-HLA antibodies are preformed antibodies to HLA antigens.[11,15,16] Renal transplant recipients can develop anti-HLA antibodies as a result of sensitization events that include blood transfusions, previous transplants, pregnancies, and rarely as a consequence of infections. With widespread use of recombinant erythropoietin in ESRD patients, allosensitization due to blood transfusion has decreased considerably. Anti-HLA antibodies bind to HLA antigens expressed on the surface of donor cells, and can cause hyperacute rejection and immediate graft loss. These antibodies are particularly deleterious if they are directed at HLA class I antigens, and are able to activate the complement cascade by binding to complement proteins.

Panel reactive antibodies

The anti-HLA antibodies can be detected by testing the transplant recipient's serum against a panel of cells that express potential donor HLA antigens present in the local population. The results are expressed as percentage of donor cells showing a positive test with the recipient's serum. Anti-HLA antibodies determined in this manner are also known as panel reactive antibodies (PRA), which provide the information on sensitization status and robustness of the immune responses of the transplant candidate.

The PRA test is performed using the National Institutes of Health recognized complement dependent microlymphocytotoxicity assay (NIH-CDC). The NIH-CDC assay involves determination of the donor's T and B cell lympholysis induced by anti-HLA antibodies in the recipient's serum in the presence of complement.[11] Low-level anti-HLA antibodies can be detected by using more sensitive assays, such as, anti-human globulin (AHG) enhanced NIH-CDC assay, enzyme-linked immunosorbant assay (ELISA), or by flow cytometry using HLA antigen-coated beads.[16] The anti-HLA antibodies can be further characterized in a high-risk or highly sensitized recipient. Transplants from donors bearing these HLA antigens should be avoided in such patients. Highly sensitized individuals (PRA > 50%) are more likely to experience acute rejection episodes even when unacceptable antigens are avoided. Treatment with intravenous immunoglobulin (IVIg), plasmapheresis, and the anti B-cell monoclonal antibody rituximab and alemtuzumab (Campath-1H) have the potential to lower PRA and are currently being studied.[17]

Crossmatch

Crossmatch determines the compatibility between a specific recipient and a donor, and is the final pre-transplantation immunologic screening step.[11] The test involves testing recipient's serum against donor T and B cells to detect any preformed antibodies against donor's lymphocytes. Conventional crossmatching is done by NIH-CDC assay. Sometimes, IgM autoantibodies present in recipient's serum can give a false-positive result in the CDC crossmatch test. To overcome this, the recipient's serum is pretreated with dithiothreitol (DTT), which

disrupts the S–S bonds in IgM autoantibodies and inactivates them. A negative crossmatch with DTT pretreatment is, thus, able to differentiate between preformed autoantibodies and alloantibodies.

A positive T-cell crossmatch after DTT treatment is indicative of preformed alloantibodies against donor antigens and is a contraindication to renal transplantation from that specific donor. The sensitivity of the crossmatch has now been enhanced many-fold by antihuman globulin-enhanced ELISA assay and flow cytometry crossmatch techniques. These tests are especially useful for patients undergoing re-transplant, and those who are highly sensitized.

Immunobiology of allograft rejection

It is essential to understand the mechanisms involved in allograft rejection in order to understand the logistics of immunosuppressive drug therapy for maintaining a successful transplant.[7,18] Following surgical implantation of the renal allograft, antigen-presenting cells (APCs), which are macrophages, dendritic cells, endothelial cells, and B cells of the recipient, process donor alloantigens. The APCs process these alloantigens into peptides, which are then loaded onto the cell surface in the groove of HLA molecules. These APCs then leave the graft and migrate to secondary lymphoid tissues where they activate naive T cells that have specific receptors for HLA–allopeptide complexes (indirect allorecognition). Additionally, T cells are also able to directly recognize donor APCs bearing HLA molecules loaded with self-peptide (direct allorecognition). Pathways of direct and indirect allorecognition are shown in Figure 28.2. The ability of T cells to recognize and respond to alloantigens occurs in a manner similar to their ability to respond to other foreign antigens, such as infectious agents. CD4+ T cells are involved in recognition of alloantigens presented with HLA class II, whereas CD8+ T cells recognize those presented with HLA class I molecules.

The immune response of T cells to alloantigens occurs in a three signal sequences (Figure 28.3). Signal 1, or the antigenic signal, is characterized by the interaction between HLA–allopeptide complex and CD4+ T-cell receptor. Signal 2 is a costimulatory signal given through a number of pathways, which include the CD40/CD40-ligand interactions that increase γ-IFN production and upregulate B7 expression and subsequently the B7/CD28 interaction that is a powerful costimulator of T-cell activation. When T cells receive both signals (I and II), there is an activation of a number of enzymes, followed by an increase in cytosolic calcium. Cytosolic calcium binds to calcineurin, which turns on the nuclear factor activating transcription (NFAT), which is translocated to the nucleus and promotes synthesis of cytokines such as interleukin 2 (IL-2) and γ-IFN. IL-2 enhances the synthesis of other cytokine genes, such as IL-3, IL-4, IL-5, IL-6, and tumor necrosis factor-α (TNF-α). Signal III consist of secreted IL-2

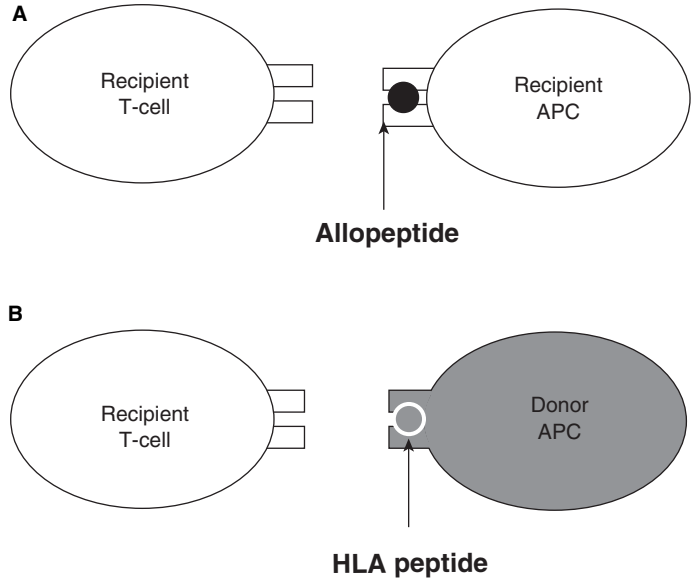


Figure 28.2 Allorecognition process. (A) Indirect recognition of the allograft is mediated by the recipient's T cells with receptors specific for allopeptides processed and presented by the recipient's antigen-presenting cells (APCs) in association with self HLA class I or class II molecules. (B) Direct recognition of a grafted organ is mediated by the recipient's T cells with receptors specific for the allogeneic HLA class I or class II molecules combined with HLA peptide present on the donor's APCs.

interacting with the IL-2 receptor present on the surface of these T cells. IL-2 interacts with IL-2R in autocrine and paracrine pathways. This interaction stimulates a series of enzymatic reactions that eventually drive the cell cycle into division, resulting in clonal expansion and differentiation of graft reactive CD4+ lymphocytes. However, prior to cell division, de-novo synthesis of purine and pyrimidine nucleotides occurs in the T cells. If T cells receive only signal I but no signal II, they undergo apoptotic cell death.

Stimulated CD4+ T cells provide help to CD8+ T cells, B cells, macrophages, NK cells, and platelets through secreted cytokines. All these stimulated cells mediate graft destruction (Figure 28.4). CD8+ T cells, also known as cytotoxic T cells, secrete granzyme and perforins that cause destruction of the allograft. IL-3, IL-4, and IL-5 stimulate B cells that produce antibodies against donor antigens. IL-1 and TNF-α facilitate activation of macrophages and other inflammatory cells, and IL-6 stimulates platelets. IL-6 also appears to be critical in reversing the action of regulatory T cells that might prevent allograft rejection. Allografts containing disparate HLA antigens generate a stronger signal I, and are more likely to experience rejection compared with those more closely related to the recipient's HLA.[11] These activated T cells and other inflammatory cells (B cells, macrophages, and platelets) eventually leave the lymph nodes and enter the circulation to infiltrate the allograft, where they cause allograft damage and inflammation. The mechanisms by which these cells migrate into the allograft are still not fully understood.

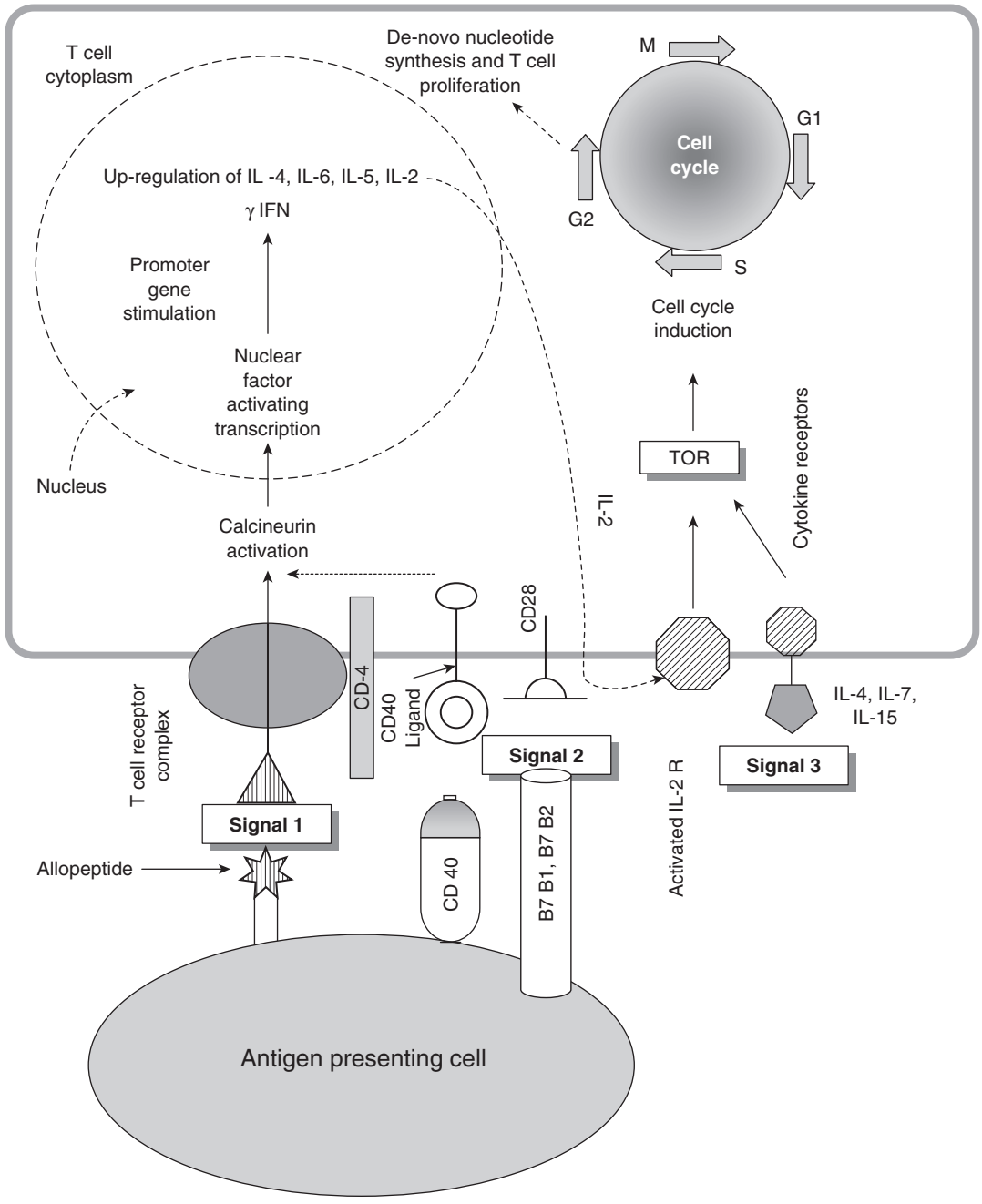


Figure 28.3 Signal pathways to T-cell activation. Signal I is the interaction between APC-presenting allopeptides and CD4+ T-cell receptor. Signal II is a costimulatory signal arising from interaction between B7-1/B7-2 and CD28, and CD40 and CD40 ligand. Upon receiving both signal 1 and 2, there is an increase in cytosolic calcium that activates calcineurin and promotes synthesis of IL-2 and other cytokines. IL-2 activates IL-2 receptor (IL-2Rα) on the cell's surface, sending signals to activate the target of rapamycin (TOR) and stimulates cell cycle synthesis. Prior to cell division, there is de-novo nucleotide synthesis. (Based on Halloran.[18])

Immunosuppressive therapies

Immunosuppressive drugs are used to overcome immunologic barriers to transplantation.[18] The drugs that are used at the time of renal transplantation to suppress unwanted allograft-directed immune responses are referred to as induction agents. Those that are used for long-term maintenance of the immunosuppressive state in the recipient are called maintenance immunosuppressives. Because of clinical implications, these two sets of therapies will be considered separately.

Induction therapies

Induction agents include polyclonal and monoclonal antibodies and are also referred to as biologic agents. These therapies target the cell surface molecules of the immune competent

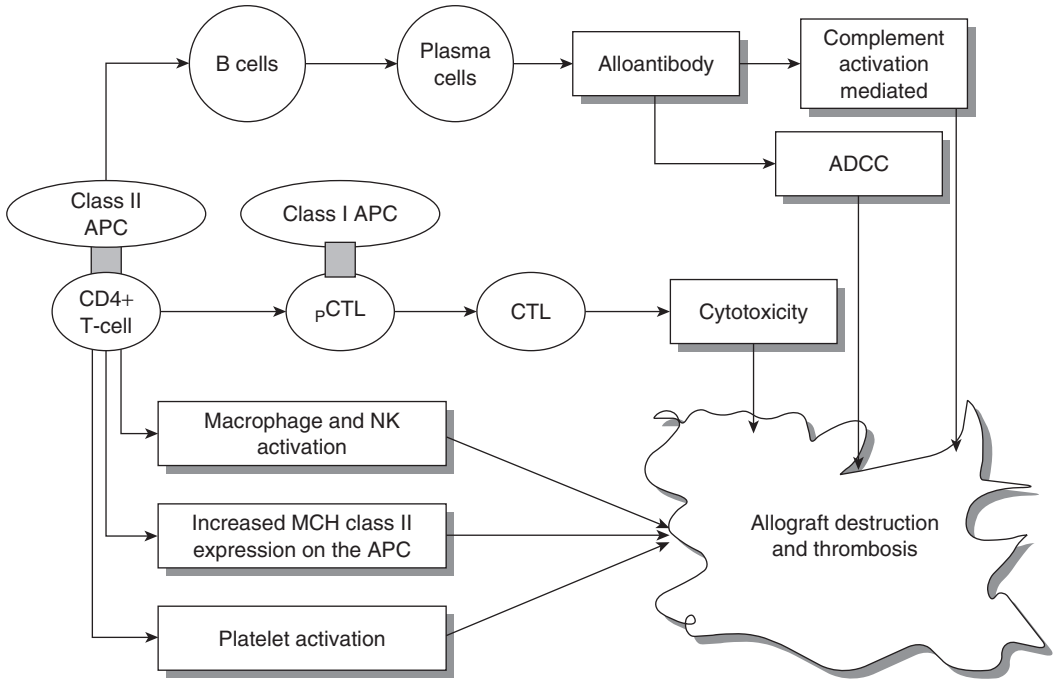


Figure 28.4 Orchestration of different cells in causing allograft destruction. Interaction between APCs and CD4+ T cells resulting in a secretion of a number of cytokines that stimulate a number of cells causing graft destruction. Activated B cells mature into plasma cells, which secrete alloantibodies that mediate antibody-dependent cell cytotoxicity (ADCC) and complement mediated allograft damage. Activated CD8+ T cells or cytotoxic T cells (CTL) secrete granzyme and perforins that cause direct damage to the allograft cells. Activated macrophages and dendritic cells increase efficiency of allopresentation to CD4+ T cells. Activated platelets add thrombotic component to the graft destruction.

cells. Polyclonal antibodies include antithymocyte globulin raised in horses (ATG) and rabbits (Thymoglobulin). Both of these commercially available agents contain antibodies against multiple T-cell surface antigens (CD2, CD3, CD4, CD5, CD8, CD11, CD18, CD28, CD45, and T-cell receptor), and cause extensive T-cell depletion. Monoclonal antibodies include murine monoclonal anti-CD3 (OKT-3) and anti-IL-2R antibodies (dacluzimab and basiliximab). OKT3 effaces T-cell receptor complex from all T cells, rendering them incapable of recognizing alloantigens. OKT3 is rarely used as an induction agent these days due to its extensive side-effect profile. Anti-IL-2R antibodies bind to the α-chain of IL-2 receptor, making it unavailable for IL-2 binding and subsequent cell division (blocking signal III).

Maintenance immunosuppressive drugs

These are pharmacologic agents capable of acting on targets inside the T cells (Figure 28.5), and maintaining a state of immunosuppression for the long-term viability of the allograft. These agents include calcineurin inhibitors, such as cyclosporine A (CsA) and tacrolimus (FK506), antiproliferative agents such as mycophenolate mofetil (MMF), azathioprine and sirolimus, and corticosteroids (prednisone, prednisolone, and methylprednisolone).

Calcineurin inhibitors

CsA and tacrolimus bind to cyclophilin and FK506-binding proteins (FKBP-13), respectively, and inhibit the activity of the enzyme calcineurin.[19] NFAT translocation to the nucleus is consequently blocked, preventing transcription of IL-2 and other cytokine genes.

Antiproliferative agents

Azathioprine and MMF act as antiproliferative agents by inhibiting de-novo purine synthesis required for cell division. Mycophenolic acid (MPA), the active metabolite of MMF, is a potent, selective, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase, an enzyme required for de-novo purine synthesis. MPA inhibits T- and B-lymphocyte proliferation that is critically dependent upon de-novo purine synthesis. Additionally, MPA alters the expression of cell surface adhesion molecules by inhibiting glycosylation of lymphocyte and monocyte glycoproteins.[18,21]

Sirolimus, previously known as rapamycin, acts on the 'molecular target of rapamycin' (mTOR), and blocks the ability of cells to enter the cell cycle.[18,22]

Corticosteroids act primarily on the APCs and inhibit their ability to produce IL-1 and other cytokines.[18,20] Many cytokine genes, including IL-2, have a glucocorticoid response element (GRE) in the 5′ regulatory region that serves as a target for corticosteroid and intracellular glucocorticoid receptor

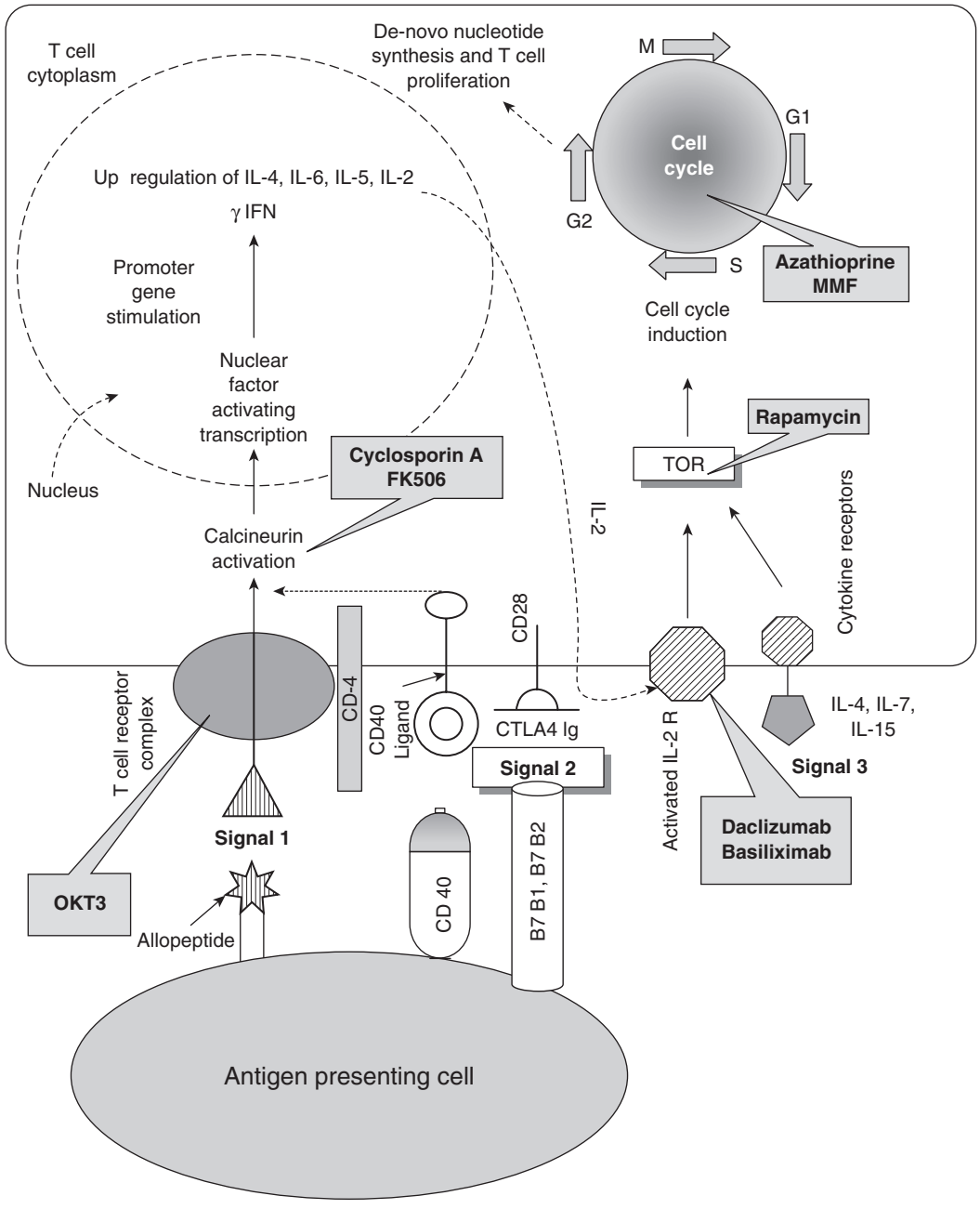


Figure 28.5 Mechanism of action of common immunosuppressives used in clinical practice. CsA and FK506 inhibit calcium-activated calcineurin, blocking interleukin-2 (IL-2) gene promotor action and synthesis of IL-2 (signal I blockage). Steroids inhibit IL-2 synthesis and also have an inhibitory action on APCs (not shown in the figure). Rapamycin binds to TOR and blocks the entry of cell into entering cell cycle after IL-2 binds to IL-2R. Mycophenolate mofetil and azathioprine inhibit purine synthesis required for cell division. CTLA 4Ig inhibits the interaction between CD40 and CD40 ligand (blocking signal 2). OKT3 effaces T-cell receptor from the cell surface. IVIg and Thymoglobulin (not shown) have antibodies to the multiple cell surface receptors on T cells. MMF, Mycophenolate mofetil; FK506, Tacrolimus; TOR, target of rapamycin (Based on Halloran.[18])

complex. Binding of this complex with GRE blocks transcription of cytokines. High-dose methylprednisolone causes lympholysis and is, therefore, useful for the treatment of AR.

Novel immunosuppressive drugs

Several promising immunosuppressive agents are currently in different phases of clinical trials,[23] including Campath-1H (alemtuzumab), a humanized monoclonal antibody that targets the CD52 antigen on lymphocytes, monocytes, macrophages, and natural killer cells. Binding of CD52 antigen by the antibody and complement results in cell lysis. When used as an induction agent, Campath-1H is associated with a reduction in incidence of AR.

Antibodies to CD 40 ligand interact with CD40 antigen on dendritic cells and B cells, thus blocking the costimulation

pathway. This drug was found to be useful in preventing rejection in animals. FTY 720 is a novel immunosuppressant that produces profound lymphopenia by sequestration of lymphocytes in secondary lymphoid structures. These drugs are yet to be approved by the US Food and Drug Administration (FDA) for prevention of rejection in transplant recipients.

Indications and contraindications to transplantation

Most children with ESRD qualify as candidates for renal transplantation. Although there is no clear agreement on the contraindications to renal transplantation in children, the generally practiced absolute and relative contraindications to renal transplantation are listed in Table 28.2.[4,24] Patients with childhood malignancies should be free of recurrence for a period of 2–5 years, based on the site and type of malignancy.[25] Children with oxalosis should be considered for a combined liver and kidney transplant.[26,27] Patients with hepatitis C infection should be evaluated by a hepatologist prior to listing. Evaluation should include a liver biopsy for staging of hepatitis C disease and consideration for treatment with α-INF on dialysis prior to transplantation. Post-transplant immunosuppressive regimens for hepatitis C patients should be chosen carefully, since induction with T-cell depleting agents can result in fulminant progression of hepatitis C.[28]

Children with multiple congenital anomalies, or severe mental retardation, pose an ethical dilemma. Input from the family, an ethicist, a patient advocate from the community, in addition to a multidisciplinary medical team is necessary in weighing the option of renal transplantation. Non-adherence to medical treatment is an important barrier to successful outcome of renal transplantation.[29] Non-adherence of the patient on dialysis is considered a relative contraindication to renal transplantation in many centers. However, there is a limited consensus on defining non-adherence to medical therapy, which can range from poor observation of phosphorus or fluid balance to not returning to in-center hemodialysis.

Table 28.2 Contraindications to renal transplantation in children

Absolute contraindications	Relative contraindications
Human immunodeficiency virus (HIV) infection	Multiple congenital anomalies
Untreated malignancy	Untreated hepatitis C infection
Oxalosis	Severe mental retardation
Multi-organ failure	Poor compliance with medical regimens
Progressive neurologic illness	
Active infective state	
Chronic hepatitis B infection	

Pre-transplant evaluation of the recipient

The goal of pre-transplant evaluation is aimed to ensure and enhance the patient's suitability as a transplant recipient. Table 28.3 lists the principles of pre-transplant evaluation applicable to children.

Urologic evaluation and preparation

Approximately a third of children undergoing renal transplantation have some form of structural abnormalities or dysfunction of the urinary tract, such as posterior urethral valves, vesicoureteric reflux, prune-belly syndrome, neurogenic bladder, Hinman syndrome, or exstrophy of the bladder. These abnormalities can contribute to failure of the graft function.[30,31] Consequently, urologic evaluation and management is an important preparatory step for children being evaluated for renal transplantation. Such an evaluation may include examination of the lower urinary tract anatomy by contrast voiding cystourethrogram (VCUG), assessment of bladder compliance and emptying function by postvoid ultrasound, and uroflow and urodynamic studies. Any necessary urinary tract reconstructive surgery should be done ahead of transplantation.

Identifying comorbid conditions

Pre-transplant evaluation should be aimed at identifying clinical, physiologic, psychological, and socioeconomic conditions that may impact the successful outcome of a renal transplant. Patients should be screened for chronic infections, which may be regarded as contraindications to renal transplantation. Native nephrectomies for chronic infection of the kidneys, severe nephrotic syndrome (congenital or idiopathic FSGS), polyuria with severe fluid and electrolyte wasting, polycystic kidneys, intractable hypertension, large renal masses, or nephrolithiasis may be necessary in some children. NAPRTCS data suggest that about 25% of children undergo native nephrectomies in preparation for renal transplantation.[1]

Determining the cause of ESRD

Establishing the cause of ESRD is important, since many diseases have the potential for recurrence in the transplanted kidney. This includes focal segmental glomerulosclerosis (FSGS), atypical hemolytic uremic syndrome (HUS), and membanoproliferative glomerulonephritis (MPGN). In such cases, strategies should be developed to optimize the timing of transplant, and monitor for recurrence and treatment. The potential for recurrence of primary glomerular diseases is not considered a

contraindication to transplantation, but some centers do not use living donors if the risk of recurrence is high.

Immunologic evaluation

Immunologic evaluation is discussed above, and includes determining the blood group and HLA antigens and identifying anti-HLA antibodies by PRA testing.[7,11] The final step is to perform a crossmatch with the prospective donor.

General health maintenance

Age-appropriate immunizations, including hepatitis B, varicella, and Pneumovax[23] vaccines, should be provided to children prior to transplantation procedure.[32,33] Growth and nutritional status should be optimized.

Psychosocial evaluation

Non-adherence to medical therapy is an important cause of graft failure, particularly in adolescents.[29] Therefore, the child and family's ability to comply with long-term immunosuppression and medical therapy should be assessed and documented. The family support system may need to be strengthened in some cases in order to ensure an optimal long-term transplant outcome.

Donor evaluation

Living renal transplant donation can be from either an individual who is related to the child (parents or siblings older than 18 years of age), or an unrelated person with a significant emotional bond with the child.[34,35] It is generally recommended that a physician not familiar with the child's needs should evaluate living donors to ensure that they are medically suitable to donate a kidney. An outline of donor work-up is shown in Table 28.4. The UNOS ad hoc living donor committee has published living kidney donor evaluation guidelines.[3]

Living donor (related and unrelated) allografts have a longer half-life compared with those obtained from the deceased donors.[1,3] This is thought to be secondary to relatively healthy organs, and elimination of cold ischemia time necessary for deceased donor kidney preservation. Increased cold ischemia time increases the risk of AR as a result of enhanced expression of HLA antigens and adhesion molecules on the surface of endothelial and renal tubular cells.[36]

Table 28.3 Pre-transplant evaluation and preparation of the recipient

1. History and physical examination:
   - Determine the cause of ESRD if possible
   - Identify comorbidities
   - GU, lower spine, perineum, and neurologic examination
   - Nutrition evaluation and optimization
   - Age-appropriate immunizations
2. Psychosocial evaluation and counseling of the child and family
3. Immunologic evaluation: ABO and HLA typing; screening for anti-HLA antibodies
4. Evaluation for exposure to infections: antibodies to viral infections (CMV, EBV, HSV, HIV, varicella zoster virus, hepatitis B and C); hepatitis B surface antigen; serologic tests for syphilis; chest X-ray; and tuberculin testing
5. Urologic evaluation: urinalysis and urine culture; ultrasonography, including postvoid images of the bladder, voiding cystourethrogram; voiding diary; uroflow; urodynamics; and rarely cystoscopy in patients with complicated urologic problems
6. Optional: neurocognitive evaluation; hematologic evaluation if suspected of being at risk for thrombosis; cardiac, pulmonary, dental, and ophthalmologic examination, as indicated
7. Financial screening and counseling

Table 28.4 Evaluation of living related, unrelated, and altruistic donor

1. Psychosocial screening and counseling
2. Detailed history and physical examination
3. Renal function tests, including 24-hour urine collection for protein and creatinine measurement, liver function tests, screening for diabetes
4. Age-appropriate screening for cardiovascular health and malignancies
5. ABO, Rh, and HLA typing
6. Screening for infections: antibodies to viral infections (HIV, CMV, EBV, hepatitis B and C); hepatitis B surface antigen; serologic tests for syphilis; chest X-ray; and tuberculin testing and screening for infection pertaining to geographic area of origin
6. Renal and renovascular anatomy: renal ultrasound, renal angiography, or spiral CT scan or MRI of kidneys with MRA and MRV

Surgical procedure

Living donor nephrectomy

Kidney from a live donor can be procured either by traditional open donor nephrectomy (ODN) or by laparoscopic donor nephrectomy (LDN). LDN was first used to procure kidneys for the purposes of transplant in 1995.[37] Today, LDN is being offered at many of the transplant centers in the United States. LDN has shortened the hospital stay, decreased the need for analgesia, and has hastened the recovery for the donors. Short-term graft outcomes for kidneys obtained by LDN are comparable to those obtained by ODN. A recent analysis of UNOS data shows a higher incidence of delayed graft function and AR in the young recipients (0–5 years of age) of kidneys obtained by LDN, raising a concern for the use of this practice in young recipients.[38]

Organ implantation procedure

The renal allograft is placed extraperitoneally in the iliac fossa in children weighing greater than 20 kg.[39] The renal artery and vein from the donor are connected to the child's common iliac or external iliac artery and vein, using an end-to-side anastomosis technique. In infants and young children less than 20 kg, the donor kidney is placed intraperitoneally in the abdomen. In this case, the renal artery and vein of the allograft are connected to the side of the aorta and inferior vena cava, close to the bifurcation (Figure 28.6). These general surgical principles are applied to both living as well as deceased donor renal transplants. Meticulous detail to the vascular anastomosis technique is required in children. This is especially important in young infants, where the vessel size is considerably smaller than that of adults and older children.

The ureter is generally connected to the bladder using ureteroneocystostomy. Attention needs to be paid to preserving the arterial supply of the lower segment of the ureter. Interruption of blood supply to this ureteral segment may result in ureteral ischemia and consequent urinary leaks, or ureteral stricture.

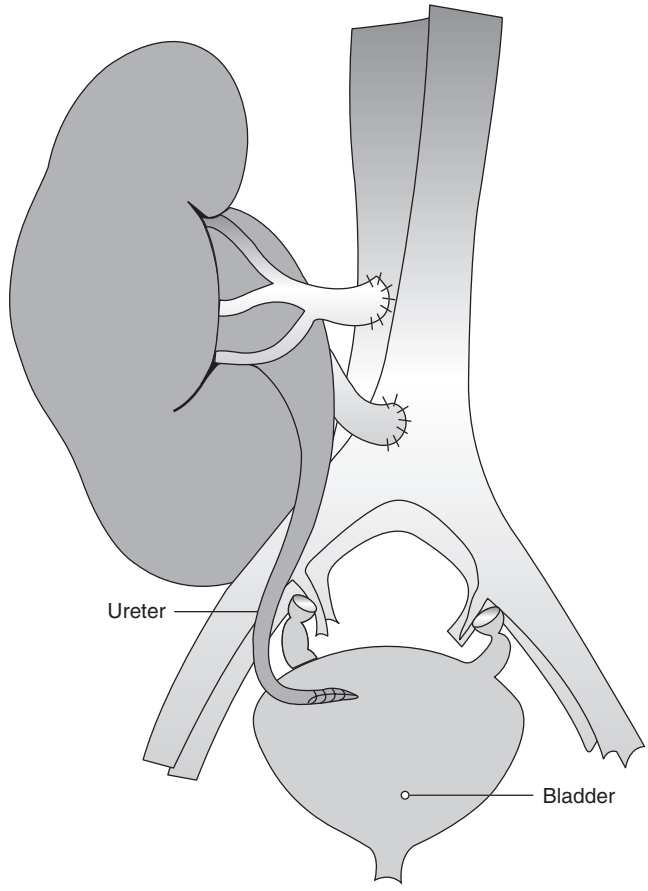


Figure 28.6 Surgical anastomosis and placement of an extraperitoneal renal allograft. The donor renal artery and vein are connected to the lower end of the recipient's aorta and inferior vena cava, respectively.

Perioperative transplant management

Fluid and electrolytes

Some children may need to be dialyzed prior to renal transplantation in order to optimize fluid and electrolyte status, particularly if they are to receive an organ from a deceased donor; however, hypovolemia should be avoided. Except in polyuric children, preoperative intravenous fluids are not necessary in most cases. Close attention needs to be paid to intravascular volume in the operating room by infusion of crystalloid and colloid solutions.

After vascular anastomosis, an adult kidney can sequester up to 250 ml of the recipient's blood volume. This may represent a significant proportion of total blood volume in an infant, or a small child (blood volume of a 10 kg child is 80 ml/kg, 800 ml). As a result, appropriate intraoperative fluid management is critical in infants and young children.[40] Central venous pressure (CVP) should be maintained between 10 and 15 cmH_2O prior to removal of the aortic cross clamps to ensure good blood flow to the allograft as a low-flow state can promote allograft thrombosis. Pressor agents such as dopamine may be required in order to help maintain adequate blood pressure. Many centers use mannitol (0.5–1 g/kg) and furosemide in a dose of 1–2 mg/kg at the time of removal of the cross clamp to induce diuresis in the transplanted organ. Sometimes, an intra-arterial vasodilator such as verapamil may also be given in order to overcome renal arterial vasospasm.

Postoperative fluid and electrolyte management includes replacement of insensible losses and replacement of urine output with an appropriately constituted fluid. Five percent dextrose solution can be used to replace insensible fluid losses, and replacement of urine output can be achieved with a solution with an electrolyte composition approximating that of urine electrolyte analysis. Further adjustments in electrolyte

composition of the replacement fluids should be based on serum and urine electrolyte analysis. In order to facilitate renal function of the allograft, CVP should be maintained in the range of 8–10 cmH_2O in the first 24 hours after transplantation.

Fluid and electrolytes status needs to be monitored and managed carefully in patients with delayed graft function. Need for dialysis should be considered carefully in such cases. Attempts at aggressive fluid removal during dialysis should be avoided, since this can result in hypovolemia and superimposed acute tubular necrosis (ATN), further impeding the recovery of function in these grafts.

Immunosuppressive management

The goal of immunosuppressive therapy is to prevent allograft rejection, while avoiding complications of immunocompromise, such as infections and malignancy. Immunosuppressive therapy is most intense in the first few weeks to few months after renal transplantation.

Most centers use some form of induction therapy at the time of transplantation. Induction regimens usually consist of monoclonal or polyclonal antibodies, and are indicated in high-risk patients (highly sensitized re-transplants and patients with delayed graft function). Infants and young children may have a propensity for more intense allograft-directed immune responses and usually metabolize immunosuppressive medications at a faster rate than adults.[41] Therefore, they may benefit from induction therapies.

CsA, tacrolimus, prednisone, azathioprine, MMF, and sirolimus are used in various combinations for maintenance immunosuppression, and are initiated around transplant surgery. Steroids have been traditionally used in most transplant immunosuppression protocols. Intravenous steroids are often used intraoperatively and for the first few post-surgery days, followed by oral therapy after adequate gastrointestinal function is achieved. A combination of calcineurin inhibitor drugs (CsA or tacrolimus) and antiproliferative agents (azathioprine, MMF, or sirolimus) is initiated soon after transplantation. In order to avoid nephrotoxicity in patients with delayed graft function, calcineurin inhibitors should not be initiated until satisfactory allograft function is established. The use of CsA as a primary immunosuppressive agent has been largely replaced by tacrolimus in recent years.[1] Similarly, MMF is used more widely now, in place of azathioprine. Sirolimus is also being selectively used in pediatric renal transplantation.[42–46] Recent NAPRTCS data indicate that at 1 month after transplantation, 67% of children were receiving tacrolimus, 57% MMF, and 20% CsA.[1]

Because of a high-toxicity profile associated with long-term steroid use, attempts have been made to curtail or eliminate steroid use in long-term maintenance immunosuppressive protocols. In the earlier studies employing CsA and azathioprine, steroid withdrawal was associated with high incidence of acute rejection.[47–49] Steroid withdrawal in more recent studies has been more successful in protocols, especially using tacrolimus, in combination with either MMF or azathioprine.[50–52] A multicenter study evaluating steroid avoidance protocol in children using tacrolimus, MMF, and extended induction with daclizumab is currently underway.[53]

The choice of immunosuppressive protocol used in any renal transplant center is often dictated by the physician's and the transplant team's familiarity and experience with the particular pharmacologic agents. Change in protocols is generally an evolutionary process, based on the need to seek better transplant outcomes and minimize the complications. All members of the transplant team should be familiar with the mechanism of action of various drugs, drug interactions, dosages, and side-effect profiles of the immunosuppressive agents used at their transplant center. Inadvertent use of drugs that interact with immunosuppressive medications can result in significant complications and morbidity. Prevention and treatment of infections should be an integral part of immunosuppressive management of transplant patients and should be incorporated in the protocol.

The immunosuppression protocol followed currently at Children's National Medical Center consists of a single preoperative dose of MMF in low-risk recipients, followed by the first dose of anti-IL-2R antibody given intraoperatively. In high-risk transplants (patients with high PRA, re-transplants, and in whom a delayed graft function is anticipated), Thymoglobulin is initiated either preoperatively or intraoperatively. Intravenous methylprednisolone (10–15 mg/kg) is given in the operating room. After establishing good renal function in the postoperative period, FK506 is started and MMF and steroids are continued. Anti-IL-2R antibody treatment is completed in patients in whom it has been started. Similarly, those receiving Thymoglobulin induction complete their anticipated 3–7 doses, based on the allograft function. Steroid dose is gradually tapered, and by the end of 3 months most children receive prednisone at 0.1 mg/kg/day.

Anti-infective prophylaxis

Anti-infective prophylaxis is important in preventing opportunistic infections.[54–56] The American Society of Transplantation has published guidelines for the prevention and management of infectious complications of solid organ transplantation.[57] Trimethoprim–sulfamethoxazole (Bactrim, Septra) is used for prophylaxis against *Pneumocystis carinii* pneumonia (PCP) infection and urinary tract infections.[54] The usual dose is 5 mg/kg/day (based on the trimethoprim component, maximum daily dose is 320 mg) given on a thrice-weekly schedule, such as Monday–Wednesday–Friday or on three consecutive days per week. Duration of PCP prophylaxis is usually for 4–6 months, but may need to be prolonged, depending upon the intensity of immunosuppression and therapy of AR episodes. In children allergic to trimethoprim–sulfamethoxazole, inhaled (>6 years of age) or IV pentamidine (<6 years of age) can be used once a month. The dose of inhaled pentamidine is 300 mg via Respirgard II inhaler, and the dose of IV pentamidine is 4 mg/kg/dose. Trimethoprim–sulfamethoxazole also serves as prophylaxis for urinary tract infections (UTIs), nocardia, and toxoplasmosis. Suppressive

therapy with trimethoprim–sulfamethoxazole can be continued in children at high risk for UTI.[58] In order to prevent fungal infections, nystatin, 4–6 ml 3–4 times a day, is prescribed for swishing and swallowing. Nystatin prophylaxis is continued for 4–6 weeks post-transplantation.

Prophylaxis against cytomegalovirus (CMV) infection is necessary for patients at high risk of developing the infection. Oral ganciclovir, or valganciclovir, is adequate in most patients, and is continued for 3–6 months. Valganciclovir is preferred, since it offers better absorption and bioavailability than oral ganciclovir. The dose of valganciclovir is 13.2 mg/kg/day.[59] Herpes simplex virus (HSV) infections can be prevented by low-dose acyclovir in children who are not receiving ganciclovir or valganciclovir.

Post-transplant monitoring

Since the risk of acute rejection is highest in the first 3 months post-transplantation, close monitoring of renal function is essential during this period. Additionally, patients should be carefully monitored for side effects of therapies used and for infections. Surveillance for malignancy should be included in the long-term management of these patients.[60] Frequency of monitoring decreases with time, and as the risks of rejection and infection wane.

Judgment regarding adequacy of immunosuppression is usually based on careful clinical and laboratory monitoring for signs of acute rejection and infections. Easily assessed immunologic markers indicative of acute and chronic allograft rejection, as well as adequacy of immunosuppression, are lacking. Measurement of cytokines (granzyme and perforins) or chemokines in the urine by polymerase chain reaction (PCR) has recently been shown to correlate with acute rejection and may pave the way for future immune monitoring of allograft status.[61,62] The gene profiling of blood and biopsy tissue by microarray technology also holds some promise in differentiating patients with acute rejection from patients with stable graft function.[63] These tests, however, are not yet available for routine clinical purposes. The Cylex assay has recently become available for monitoring ATP generation by the peripheral CD4+T-cells in transplant recipients. This test may offer a relatively rapid assessment of T-cell immunity in transplant recipients.[64]

Complications of transplantation

Delayed allograft function

Delayed graft function (DGF) refers to transplants that fail to function after blood flow through the allograft is established. DGF is more common in organs transplanted from deceased donors, in particular in those with increased cold ischemia time. The risk factors for DGF in children include deceased organ transplant, patients with previous transplants, patients receiving more than 5 transfusions, African-American ethnicity, and patients with native nephrectomies.[1] A higher incidence of DGF has also been observed in young recipients (0–5 years) transplanted with laparoscopically procured kidneys.[38] Other well-known causes of DGF include hyperacute rejection, acute renal arterial or venous thrombosis, ATN, and rarely HUS. Urinary obstruction due to blood clots, urine leakage, and obstructed Foley catheter may also present as DGF or acute deterioration of graft function. DGF increases the risk of AR, and has deleterious effects on long-term graft survival.[38] NAPRTCS data suggest that the relative risk of graft failure due to DGF was 6.02 in recipients of deceased donor grafts vs 2.58 in recipients of live donor grafts.[65]

Prompt management of primary DGF is essential because of the high risk of allograft loss. Urinary obstruction should be ruled out by a renal ultrasound study, and graft blood flow and function assessed by MAG-3 nuclear renal scan and/or Doppler renal ultrasound. If hyperacute rejection is suspected, or the cause of DGF is unclear, transplant renal biopsy is warranted. Presence of an adequate renal blood flow with a lagging excretory function is generally suggestive of ATN.

Surgical exploration may be necessary if vascular thrombosis is suspected. ATN is managed conservatively. Dialysis therapy may become necessary in such patients. Calcineurin inhibitors and other nephrotoxic drugs should be avoided. The use of sirolimus delays the recovery from DGF, and it should not be used.[66] Alternative immunosuppressive drugs, such as anti-IL-2 R antibodies, ATG, or Thymoglobulin, may be used if allograft non-function persists. If the allograft is found to be non-viable by MAG-3 scan or biopsy, an allograft nephrectomy is warranted.

Surgical complications

Surgical complications include vascular thrombosis, lymphocele, perirenal serous fluid collection, hematoma, urinary leaks, and obstruction at the ureterovesical junction (UVJ). Vascular thrombosis is the third leading cause of graft failure in children, after chronic rejection and acute rejection. Approximately 11.6% of children in the NAPRTCS registry lost their grafts due to vascular thrombosis.[1] Patients at risk for thrombosis include those on peritoneal dialysis, those younger than 2 years of age, recipients of deceased donor grafts younger than 5 years of age, and those with cold ischemia time of greater than 24 hours. Patients with severe nephrotic syndrome may also be at an increased risk for thrombosis.

NAPRTCS data suggest that children less than 2 years of age are at highest risk for graft loss due to vascular thrombosis. About a third of graft losses occurred because of technical reasons, and graft thrombosis accounted for 23.8% of such failures. In the 2–5-year age group, the rate of graft thrombosis was also high, accounting for 16.3% of grafts lost.[67] Placement of an adult kidney in children less than 2 years of age results in unique hemodynamic challenges. High aortic blood flow is necessary in order to prevent arterial thrombosis in infants and children transplanted with adult-sized kidneys.[40]

Recent data on the genetics and pathophysiology of coagulopathies have added new insight to the understanding of thrombosis after transplantation. Several genetic mutations

causing deficiency of protein C, protein S, antithrombin III, and plasminogen, as well as those with mutations of genes for factor V Leiden, prothrombin, and methyltetrahydrofolate reductase have been described in the general population.[68] Patients with antiphospholipid antibodies are also at high risk for thrombosis. The role of these predisposing factors in post-transplant thrombosis is beginning to emerge.[69,70]

Lymphocele, perirenal serous fluid, or blood collections are common surgical complications encountered in the post-transplant period. Increased incidence of lymphocele has also been noted with the use of sirolimus.[71] Lymphoceles can resolve spontaneously and no therapy may be necessary. However, large fluid collections can cause urinary obstruction. Percutaneous aspiration or even surgical drainage may be needed in such cases. Urinary leaks are uncommon because of the current practice of using lower doses of steroids, and a closer attention to the urologic surgical techniques. Urinary obstruction at the ureteropelvic junction (UVJ) may be a manifestation of ureteral ischemia, CMV infection, polyoma virus BK infection, or rejection.[72] Ureteral stents may be used for prevention and treatment of UVJ obstruction.

Hyperacute rejection

HAR occurs due to preformed antibodies to the ABO and HLA antigens. The onset of HAR occurs within minutes to an hour of perfusing the allograft. The allograft shows signs of mottling, followed by vascular thrombosis and allograft failure. Less commonly, it can manifest as primary non-function of the graft. The incidence of HAR has decreased significantly in recent years due to availability of sensitive techniques for determining preformed antibodies in the recipients. HAR is more common in re-transplants and in patients with high PRA. Once established, HAR is not amenable to therapy and graft loss is the usual outcome.

Acute rejection

Acute rejection often occurs within the first 3 months of transplantation, but can be seen later as well. AR occurring within 1 week of transplantation is generally referred to as accelerated AR, and has a relatively poor outcome. The incidence of AR has decreased significantly due to the availability of potent immunosuppressive drugs.[73] Early diagnosis and treatment of AR is most important for both short- and long-term graft survival. The relationship between AR and long-term graft loss has been clearly demonstrated and remains an important predisposing factor for chronic rejection.[74,75] In a multivariate analysis of 290 pediatric recipients, it was demonstrated that zero AR episodes translated into better late graft survival.[76] In both adult and pediatric studies, tacrolimus-based therapy is known to be associated with fewer episodes of AR when compared with CsA-based therapy.[77–80]

The clinical features of AR include fever, oliguria, hypertension, proteinuria, and graft tenderness. In this era of modern immunosuppression, the overt clinical features of rejection are seen less often. More commonly, children present with an increase in serum creatinine on routine blood monitoring. An increase in serum creatinine of 20% above baseline should raise a concern of AR. Other clinical conditions to be considered under these circumstances include dehydration, CsA or FK506 toxicity, and urinary obstruction (Table 28.5).

Table 28.5 Differential diagnosis of post-transplant graft dysfunction

Acute increase in serum creatinine (20% above baseline)	1. Acute allograft rejection 2. Acute CsA- or FK506-induced nephrotoxicity 3. Dehydration 4. Urinary obstruction 5. Pyelonephritis
Slow increase in serum creatinine (creatinine creep)	1. Chronic allograft nephropathy 2. Chronic CsA- or FK506-induced nephrotoxicity 3. Urinary tract obstruction (organic or functional secondary to bladder dysfunction) 4. Recurrent or de-novo glomerulonephritis 5. Polyma virus BK nephropathy 6. Renal artery stenosis
Hypertension	1. Side effects of steroids, CsA or FK506 2. Acute allograft rejection 3. Transplant renal artery stenosis 4. Chronic allograft nephropathy 5. Recurrent and de-novo glomerulonephritis 6. Diseased native kidneys
Proteinuria	1. Recurrent and de-novo glomerulonephritis 2. Chronic allograft nephropathy 3. Chronic CsA- or FK506-induced nephrotoxicity 4. Acute allograft rejection

A definitive diagnosis of AR is made by biopsy of the transplant kidney. The Banff 1997 schema (Table 28.6) is the most widely used pathologic basis for diagnosis and quantification of AR.[81] The characteristic pathologic features of AR are interstitial inflammation and tubulitis (Figure 28.7). Lymphocytic infiltration of the vascular endothelium can be seen in severe cases with 'vascular AR' (Figure 28.8). Positive staining of peritubular blood vessels with C4D antibody may be observed in these patients (Figure 28.9). C4D positive staining and vascular AR are indicative of preformed anti-HLA antibodies that are complement fixing in nature and may be undetectable by standard immunologic testing. Mild AR is usually treated with intravenous methylprednisolone (10–15 mg/kg/day for 3–5 days). OKT3 (2.5–5.0 mg/day) or Thymoglobulin (1.5 mg/kg/day) are reserved for steroid-resistant moderate to severe AR, and are used for 7–14 days.[82,83] A switch to tacrolimus from CsA, or increasing the dose of tacrolimus, can also be used to treat borderline or mild AR. Other therapies, such as plasmapheresis, rituximab and IVIg, are currently reserved for treatment of antibody-mediated AR.[17]

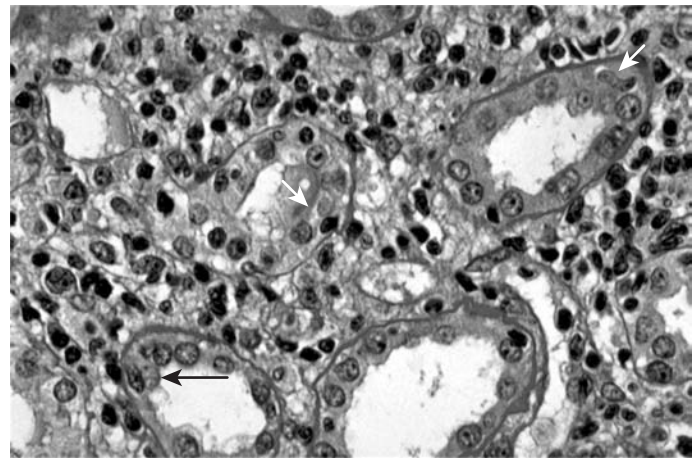


Figure 28.7 Acute renal transplant rejection. Light microscopy photomicrograph of renal transplant biopsy showing acute cellular rejection. Lymphocytes are infiltrating the interstitium and infiltrate into the tubular epithelium causing tubular injury (arrows). (Courtesy of Dr Arthur Cohen, Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California.)

Table 28.6 The Banff 97 scoring criteria

1. Normal
2. Antibody-mediated rejection:
   I. ATN-like – C4d+, minimal inflammation
   II. Capillary – margination and/or thromboses, C4d+
   III. Arterial – v3, C4d+
3. Borderline changes: 'Suspicious' for acute cellular rejection
   Mild tubulitis (1–4 mononuclear cells/tubular cross-section)
4. Acute cellular rejection (T-cell-mediated rejection):
   IA: Significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross-section or group of 10 tubular cells)
   IB: Significant interstitial infiltration (>25% of parenchyma affected) and severe tubulitis (>10 mononuclear cells/tubular cross-section or group of 10 tubular cells)
   IIA: Mild-to-moderate intimal arteritis (v1)
   IIB: Severe intimal arteritis affecting >25% of the luminal area (v2)
   III: Transmural arteritis and/or arterial fibrinoid change/necrosis of medial smooth muscle cells with lymphocytic inflammation (v3)
5. Chronic/sclerosing allograft nephropathy
   Fibrosing changes in the allograft, with or without features of true alloimmune injury
   Grade I (mild): Mild interstitial fibrosis and tubular atrophy without (a) or with (b) specific changes suggesting chronic rejection
   Grade II (moderate): Moderate interstitial fibrosis and tubular atrophy with a or b
   Grade III (severe): Severe interstitial fibrosis and tubular atrophy and tubular loss with a or b
6. Other: Changes not due to rejection

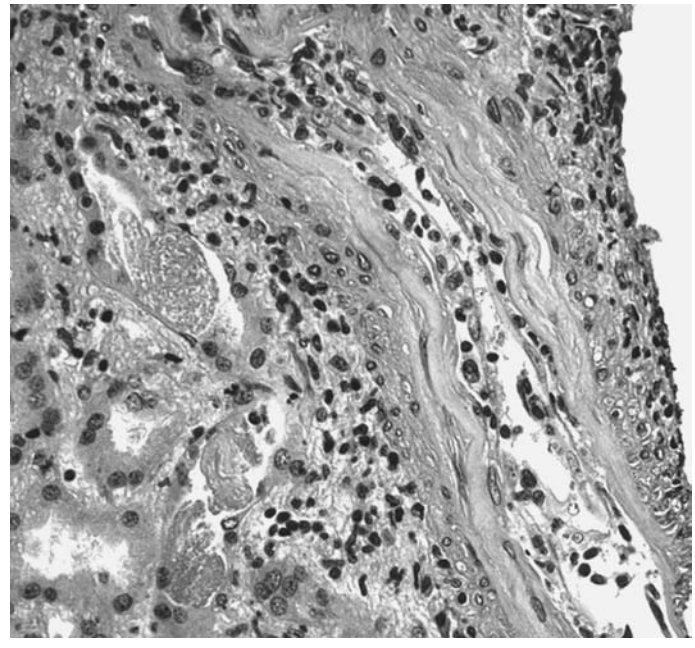


Figure 28.8 Cell-mediated acute vascular rejection. Lymphocytes are seen under vascular endothelium. (Courtesy of Dr Arthur Cohen, Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California.)

AR occurring many months post-transplant is also termed as delayed AR. This may be related to non-adherence with therapy. Medical non-adherence is prevalent in 40–50% of the pediatric transplant population and leads to allograft failure in about 25% of cases.[29] Delayed AR can be triggered in some cases by viral infection, such as CMV or EBV infection. Delayed AR is less amenable to treatment and has more deleterious effects on the allograft.

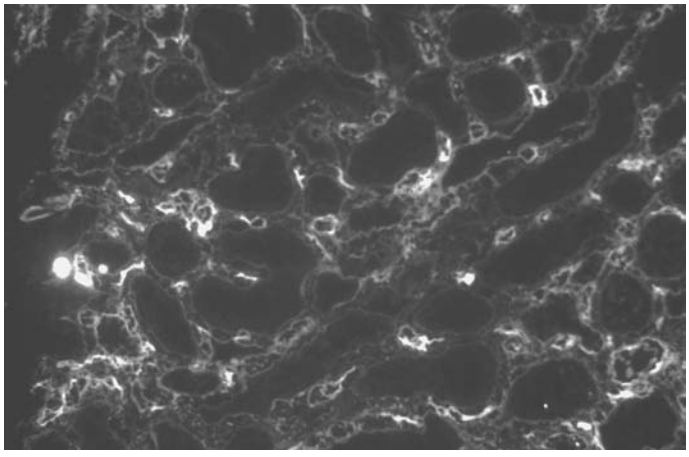


Figure 28.9 Humoral rejection. Immunofluorescence staining showing C4d positivity in the peritubular capillaries. (Courtesy of Dr Arthur Cohen, Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California.)

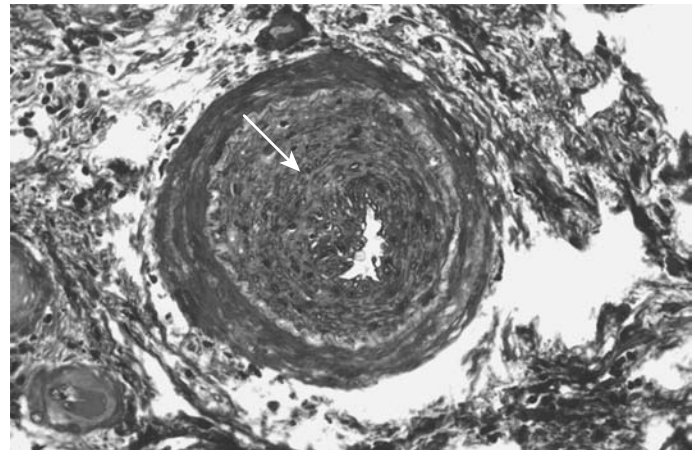


Figure 28.10 Chronic transplant rejection characterized by arterial luminal narrowing caused by intimal and medial fibrosis and disruption and duplication of internal elastic lamina (arrow). The surrounding interstitium is showing changes of fibrosis. (Courtesy of Dr Arthur Cohen, Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California.)

Chronic rejection

Chronic rejection (CR) denotes a slow, progressive deterioration of allograft function due to immunologic causes. AR is an important predisposing factor for CR, which is characterized pathologically by tubulointerstitial fibrosis, tubular atrophy, and interstitial infiltration by inflammatory cells. The arteries are thickened by intimal fibrosis and, sometimes, medial fibrosis, variable mononuclear infiltration and disruption and duplication of internal elastic lamina, leading to luminal narrowing. The glomeruli exhibit changes of chronic transplant glomerulopathy, with thickening of glomerular capillary walls, increased mesangial matrix, and cellularity (Figure 28.10).

Infection

Infections constitute the most common reason for hospitalization after renal transplantation.[1] Infectious complications after transplantation usually follow a predictable pattern.[56] In the first month after transplant, infectious complications are related to technical and mechanical problems, such as wound infections, UTIs, pneumonia, and fungal infections. Between 1 and 6 months post-transplant, common infectious events involve viral pathogens, such as CMV, Epstein–Barr virus (EBV), HSV, human herpes viruses (HHV), varicella-zoster virus (VZV), parvovirus (PV) B19, polyoma BK virus, PCP, and fungal infections.[54,84–88]

Beyond 6 months, the patterns of infections in patients on stable maintenance immunosuppression and with good allograft function are similar to that seen in the general population. Patients who develop opportunistic infections more than 6 months post-transplant are generally those who have higher serum creatinine, are receiving higher doses of maintenance steroids, or have had recurrent rejection episodes requiring intensification of immunosuppression.

Hepatitis B and C infections may become a clinical concern in long-term survivors of kidney transplants.[89,90] This may be due to reactivation of these viruses in the recipient, or as a result of infection acquired in the peri-transplant period. Tuberculosis is a serious problem in developing countries due to high risk of exposure and the immunosuppressed state of these patients.[91] Recently, deaths due to West Nile virus and rabies have been reported in transplant recipients of organs from deceased donors.[92,93] Both a high index of suspicion for infections prevalent in the community and prompt treatment are necessary.

UTIs in the allograft may be related to abnormal bladder function or vesicouretric reflux in the transplanted ureter. Most patients present with symptoms of fever, malaise, dysuria, and graft tenderness, and some may present with elevated creatinine. A recent review of 1387 adult and pediatric patients demonstrated that 13% of patients had pyelonephritis. However, no difference in the long-term outcome of patients with and without pyelonephritis was shown.[31]

Risk factors for different human herpes viruses, clinical features, diagnosis, treatment, and prevention are shown in Table 28.7. Of these, CMV infection has the most long-term deleterious effects on the allograft.[87,88]

Hypertension

Fifty to eighty percent of pediatric kidney transplant recipients develop hypertension.[94] In the immediate post-transplant period, hypertension may be related to fluid overload, high-dose steroids, and AR. Presence of diseased native kidneys, side effects of medications such as CsA, FK506, and prednisone,

Table 28.7 Post-transplant infections

Disease	Risk factors	Clinical features	Diagnosis	Treatment	Prevention
CMV	1. D+/R– 2. Polyclonal antibodies 3. AR	Viral syndrome Pneumonia Hepatitis Myelosuppression Colitis	q-PCR Pp 65 Ag assay	IV GCV CytoGam	Oral ganciclovir or valganciclovir in high-risk group Monitoring by PCR
HHV-6 and HHV-7	Net state of IS	Myelosuppression Hepatitis Pneumonia Encephalitis Exacerbates CMV/HCV	q-PCR	No data	No data
HHV-8	Net state of IS	Kaposi's sarcoma	q-PCR	Chemotherapy	No data
VZV	Net state of IS	Disseminated zoster, pneumonia	DFA for VZV	IV acyclovir until lesions are crusted	
PV B19		Aplastic anemia	q-PCR PVB19 IgM bone marrow	IVIg	No data
Polyoma BK virus	Net state of IS	Allograft dysfunction Hemorrhagic cystitis	q-PCR renal biopsy Decoy cells in urine	Decrease IS Low-dose cidofovir Leflunomide[a]	Avoid excessive IS Monitoring by PCR
PCP	Net state of IS	Interstitial pneumonitis	DFA on sputum/BAL	IV TMP-SMX	Oral TMP-SMX or aerosolized or IV pentamidine or Dapsone

D+/R–, donor positive, recipient negative; q-PCR, quantitative polymerase chain reaction; IS, immunosuppression; DFA, direct fluorescent antibody. TMP-SMX, trimethoprin–sulfamethoxazole; IV, Intravenous; BAL, bronchoalveolar lavage; PCP, pneumocystis carrnii pneumonia; IVGCV, intravenous ganciclovir; IVIg, intravenous gammoglobulin; VZV, varicella-zoster virus; PVB19, porrovious B19; HHV, human herpes virus.
[a]Reported in abstract only.

acute and chronic rejection, recurrent glomerulonephritis, and renal artery stenosis may be the cause of hypertension when it is present beyond the first few weeks post-transplantation. NAPRTCS data and other studies suggest that hypertension and use of antihypertensive drugs are significant risk factors for subsequent graft failure.[95–97] Pediatric patients treated with antihypertensive drugs during the first month after transplantation are noted to have worse linear growth over the first 2 post-transplant years compared with those patients who do not require antihypertensive medications.[1]

Hypertension is managed with a low sodium diet and antihypertensive medications. Reduction of corticosteroid dose may also improve blood pressure control. Calcium channel blockers are particularly useful in the treatment of hypertension in the early post-transplant period because of their ability to counteract the vasoconstrictive effects of CsA and tacrolimus. However, the use of calcium channel blockers may be associated with the development of significant edema. Angiotensin-converting enzyme (ACE) inhibitors may be useful in the long-term management of hypertension and in prolonging the life of the allograft due to their inhibitory effect on expression of transforming growth factor-β (TGF-β) and other growth factors, chronic tubulointerstitial scarring, and their ability to ameliorate proteinuria.[98,99] Renal artery stenosis is best treated by percutaneous transluminal angioplasty or surgical correction.[100]

Hematologic complications

Hematologic complications of transplantation include anemia, erythrocytosis, and rarely leukopenia and thrombocytopenia. Anemia after transplant may be related to bone marrow suppression secondary to MMF, azathioprine, sirolimus, CsA, or tacrolimus.[101] The incidence of hematologic complications is higher in patients on steroid-free protocols. Aplastic anemia

can occur due to PV B19 and CMV infections. Hemolytic anemia may result from recurrent or acquired HUS (secondary to drugs, infections, or hypertension).

Erythrocytosis is sometimes seen in renal transplant patients and the risk factors include male gender, retention of native kidneys, smoking, renal artery stenosis, and rejection-free course.[102] This disorder appears to occur less commonly in children.[103] Erythrocytosis can be treated with ACE inhibitors, and by phlebotomy if needed.[102] Neutropenia and thrombocytopenia rarely occur after transplant and may be due to side effects of medications, viral infections, or residual hyperparathyroidism.[104]

Growth retardation

Whereas an acceleration of growth velocity is commonly seen in the majority of children following successful renal transplantation, growth retardation may continue to be a clinical concern in some children.[105–108] Post-transplant growth velocity is better in children who receive transplant at an early age (<5 years of age), have good allograft function (serum creatinine < 2.0 mg/dl), are on minimal (prednisone dose < 0.15 mg/kg/day), or no steroids, and are on alternate-day steroids.[51]

Children with continued post-transplant growth retardation may benefit from recombinant growth hormone (GH) therapy. GH therapy is usually not considered in the first year following transplantation, since some children may demonstrate a spontaneous growth spurt. When GH therapy is used in transplanted children, linear growth is best in the first year of therapy, with a somewhat slower growth seen in the second and third years.[109] Treatment with GH should continue until full potential for growth is realized, or puberty is reached.

Treatment with GH can lead to glucose intolerance, slipped capital femoral epiphysis, and intracranial hypertension. However, the incidence of these complications is not higher than the control ESRD population.[110] The potential for increased incidence of acute rejection in children treated with GH has been seen in early clinical studies. However, larger studies have not been able to substantiate any increase in the incidence of acute rejection with GH use.[110] Patients with one or more episodes of acute rejection prior to GH therapy may be at a higher risk for AR.[109] Close monitoring of renal function and evidence for acute rejection is desirable after initiation of GH therapy. The dose of CsA may need to be increased after initiation of GH therapy.[111] Unfortunately, the FDA has not approved GH in the United States for children with growth retardation after renal transplantation, and many insurance companies may not cover treatment costs.

Recurrences of primary diseases in the allograft

Several diseases that cause ESRD in the native kidneys have potential to recur in the allograft,[112] including FSGS, atypical HUS, MPGN, IgA nephropathy, Wegener's granulomatosis, lupus nephritis, and Henoch–Schönlein purpura.

Focal segmental glomerulosclerosis

Recurrence of FSGS occurs in 30–40% of patients undergoing primary transplants and in 50–80% of patients undergoing re-transplants.[113] Graft failure occurs in 50% of these cases.[113] Clinical manifestations include massive proteinuria, hypoalbuminemia, and often the full-blown picture of nephrotic syndrome. Recurrence of FSGS may occur immediately, or weeks to months after transplantation. Predictors of recurrence include patients with FSGS who have had a rapid progression to ESRD from the time of initial diagnosis (less than 3 years), poor response to therapy, white race, and presence of mesangial proliferation in the renal biopsy.[114,115] Patients with inherited forms of FSGS due to genetic mutations have a low risk for recurrence in the transplant.[116] Live donor transplant recipients may have a higher rate of recurrence but these observations are not generally regarded as a contraindication to live donor transplantation.[117] However, if a primary transplant has been lost to FSGS recurrence, a second living donor for a repeat transplantation should be considered with great caution and with careful patient and family preparation with informed consent of the donor and the family.

A protein permeability factor has been isolated in the sera of patients with FSGS, and is reported to predict recurrence and severity of FSGS in the transplant.[118] The precise nature of this factor has not been identified. Several therapeutic interventions have been suggested in small single-center trials and anecdotal reports. These include plasmapheresis, high-dose cyclosporine, pulse methylprednisolone, and immunoadsorption with protein-A columns.[119–122] Although intensive plasmapheresis treatment for the first 6–8 weeks is generally considered, an occasional patient has been treated with long-term plasmapheresis therapy.[123] Cyclophosphamide has also been found to induce remission by some clinicians.[124]

Hemolytic uremic syndrome

Familial, or atypical, HUS can recur in the allograft, resulting in graft failure.[112] The diarrhea-associated, or 'typical,' HUS does not usually recur after transplantation.[125] Recurrent as well as de-novo HUS in renal transplants has been linked to the use of cyclosporine and tacrolimus.[126] Recurrence of HUS may be present without evidence of hemolysis or thrombocytopenia in more than half of the cases. Typically, recurrent HUS manifests shortly after starting treatment with cyclosporine or tacrolimus, with features of declining urine output, an increasing serum creatinine level, with hematuria or proteinuria. A renal biopsy establishes the diagnosis. Discontinuation of calcineurin inhibitor and plasmapheresis may help salvage some grafts. However, overall prognosis remains poor.[127] Substitution of cyclosporine for tacrolimus (or vice versa) has been recommended by some.[128] Successful use of sirolimus in this situation has also been reported.[129] De-novo transplant microangiopathy (TMA) may present in a similar manner, but is usually a manifestation of antibody-mediated rejection (AMR).[130] In our experience the TMA is usually accompanied by C4D deposits in the allograft, indicating the relation to AMR. Clearly, it is

important to differentiate the two entities, as the latter requires treatment with plasmapheresis, IVIg, and possibly Rituxan (rituximab).

Membranoproliferative glomerulonephritis

MPGN, especially type II, has the potential to recur in transplants. MPGN type I has a recurrence rate of 30–40%, whereas MPGN type II may recur in 90% of allografts.[112] The recurrence may be asymptomatic, or it may manifest as proteinuria. Usually, recurrence leads to slow deterioration of allograft function. However, it does not cause immediate graft loss.[131] Plasmapheresis and high-dose steroids may be useful in salvaging graft function in patients with rapid deterioration.[132]

Recurrent IgA nephropathy, lupus nephritis, and Wegener's granulomatosis usually do not cause allograft failure.

De-novo glomerulonephritis

De-novo glomerulonephritis, including membranous glomerulonephritis, IgA nephropathy, FSGS, collapsing glomerulopathy, steroid-resistant nephrotic syndrome, and anti-glomerular basement membrane (GBM) disease in patients with Alport's syndrome can be seen in renal transplants.[133]

Although the Finnish type of congenital nephrotic syndrome does not recur after transplantation, de-novo steroid-resistant nephrotic syndrome can recur in up to 24%.[134] Presentation with proteinuria, hypoalbuminemia, and edema may start immediately, or as late as 3 years post-transplant. Precedent infection with CMV or EBV may be seen in some. The histologic lesion in these cases is often minimal-change disease, and glomerular endothelial cell swelling has been noted in some cases. Response to steroids and cyclophosphamide is poor, and graft loss occurs in more than 50% of cases.[133] Recently, anti-nephrin antibodies have been shown to play a role in the recurrence of nephrotic syndrome.[135]

Anti-GBM disease can occur in about 5% of patients with Alport's syndrome who demonstrate complete absence of the α5 portion of type IV collagen in the basement membrane. Crescentic glomerulonephritis, with linear IgG deposits in the GBM, can lead to rapid graft loss and is a common manifestation.[136]

Side effects of pharmacotherapy

Side effects and toxicities of therapy can become an important concern in transplant patients. This may lead to non-adherence and delayed episodes of acute rejection, particularly in teenagers. Common side effects of transplant medications are listed in Table 28.8.

Metabolic complications

A number of metabolic complications can be seen in children following renal transplantation. These include hypomagnesemia, hypophosphatemia, hypercalcemia, hyperkalemia, and renal tubular acidosis. Hypomagnesemia commonly occurs from renal tubular magnesium wasting as a result of the use of CsA, tacrolimus, or diuretics.[137] Oral replacement with magnesium oxide (Mag-Ox) is usually sufficient to control hypomagnesemia.

Hypophosphatemia, resulting from residual hyperparathyroidism of ESRD, is commonly seen following renal transplantation. This responds well to oral phosphorus and vitamin D supplements. Hyperparathyroidism can take many months to resolve.[138] Sometimes, parathyroidectomy may be indicated. A recently introduced calcimimetic drug, cinacalcet HCl (Sensipar), is effective in controlling secondary hyperparathyroidism in dialysis patients.[139] Its role has not been studied in transplant patients, but seems logical.

Hyperkalemia and renal tubular acidosis may be a manifestation of CSA or tacrolimus toxicity, acute rejection, urinary obstruction, or use of ACE inhibitor drugs. Isolated hyperkalemia may be associated with co-trimoxazole (trimethoprim–sulfamethoxazole) therapy.[140]

A number of lipid abnormalities are being recognized in children after transplant, including elevated blood levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, and triglycerides, and decreased levels of high-density lipoprotein (HDL) cholesterol. These lipid abnormalities may be seen in as many as 50% of children.[141–144] The contributing factors to lipid abnormalities include use of antirejection medications (steroids, CsA, tacrolimus, and sirolimus), excessive weight gain, and IDDM (insulin-dependent diabetes mellitus). Dyslipidemia is an important contributor to cardiovascular morbidity and mortality and may contribute to functional deterioration of the graft in the adult population.[145,146] There is a paucity of data on the adverse effects of dyslipidemia and their management in children.[147,148]

Obesity

Excessive weight gain and its consequences are important considerations in the transplant recipients. The factors responsible for obesity in the general population combined with the use of steroids may play a part. Excessive weight gain may be responsible for sleep apnea, nocturnal enuresis, hypertension, dyslipidemia, and glucose intolerance. NAPRTCS data have shown an increasing prevalence of obesity in pediatric transplant recipients. Obese children between the ages of 6 and 12 years in this study were at higher risk of death compared with non-obese patients, and death was more likely to be due to cardiopulmonary disease.[149] Early and intense nutritional counseling should be undertaken to prevent this serious complication.

Diabetes mellitus

About 5% of children develop IDDM after transplantation.[150,151] The risk is somewhat higher with the use of tacrolimus than with CsA. Other contributing factors may be the repeated use of pulse steroid therapy, family history of diabetes, and excessive weight gain. Rigorous management of IDDM is essential for long-term patient and graft survival.

Table 28.8 Immunosuppressive drugs

Name of the drug	Dose	Side effects
OKT-3	<30 kg, 2.5 mg/day >30 kg, 5 mg/day for 7–14 days	Cytokine release syndrome; fever; myalgia; pulmonary edema; aseptic meningitis; increased risk of infections; and post-transplant lymphoproliferative disorder (PTLD)
Polyclonal antibodies[163]	ATG 10–15 mg/kg/day and Thymoglobulin 1.5 mg/kg/day for 7–14 days	Leukopenia; thrombocytopenia; fever, chills, and anaphylaxis; increased risk of infections and PTLD
Anti-IL-2R antibodies[164,165]	Daclizumab: 1 mg/kg on day 0, 2, 4, 6, 8 weeks; Basiliximab: <35 kg (10 mg/dose) and >35 kg (20 mg/dose) on day 0, 4.	Side effects same as placebo
Methylprednisone	10 mg/kg/day × 1 for induction at transplantation, 10 mg/kg/day for 3–5 days for treatment of acute rejection	Hypertension; hyperglycemia; fluid overload
Prednisone	2 mg/kg/day to be tapered to 0.5 mg/kg/day in 2 weeks, 0.1–0.15 mg/kg/day over 6 months	Excessive weight gain; hypertension; hyperglycemia; cushingoid features; acne; growth suppression; osteoporosis; gastric ulceration; impaired wound healing; mood change; cataracts
Cyclosporine A	6–8 mg/kg/day at the onset; adjust dose according to levels	Nephrotoxicity; hypertension; hirsutism; gingival hyperplasia; tremors
Tacrolimus	0.1–0.15 mg/kg/day; adjust dose according to levels	Nephrotoxicity; tremors; diabetes mellitus
Azathioprine	2 mg/kg/day	Myelosuppression; hepatotoxicity
Mycophenolate mofetil	1200 mg/m^2/day to a maximum of 1500 mg bid	Myelosuppression; diarrhea
Sirolimus	Loading dose 6 mg/day followed by 2–5 mg/day, adjust according to levels	Hypertriglyceridemia; mucosal ulcers; thrombocytopenia; pneumonia

Osteopenia and reduced bone mass

There are many contributing factors to reduced bone mass, including renal osteodystrophy, residual hyperparathyroidism, and the use of corticosteroids.[152] Adequate intake of calcium and vitamin D may help reduce bone loss. The use of bisphosphonates has not been studied in children.

Chronic allograft dysfunction

Chronic allograft dysfunction, also known as chronic allograft nephropathy (CAN), ultimately leads to allograft failure and the return of patients to dialysis.[153] Both immune and non-immune factors contribute to CAN. The contributing factors include CR, chronic CsA or tacrolimus nephrotoxicity (Figure 28.11), hypertension, hyperglycemia, hyperlipidemia, donor and recipient size mismatch, recipient weight, donor age, CMV infections, and recurrent and de-novo glomerular lesions. CR and chronic nephrotoxicity are the two most important causes of CAN and eventual graft failure.

Malignancy

The risk of malignancy is increased with the intensity and duration of immunosuppression. Malignancies are uncommon in the pediatric age group, but may become a problem as survival of these children increases with successful transplantation. The most important malignancy observed in children is post-transplant lymphoproliferative disorder (PTLD).

PTLD includes a spectrum of conditions that range between infectious mononucleosis and malignant neoplasia. A large body of literature exists demonstrating the pivotal role of EBV in most cases of PTLD in pediatric solid organ transplant recipients; approximately 85–90% of cases of PTLD are EBV-driven.[86,154–157] Most cases of PTLD occur in children who are seronegative for EBV at the time of transplantation. Primary

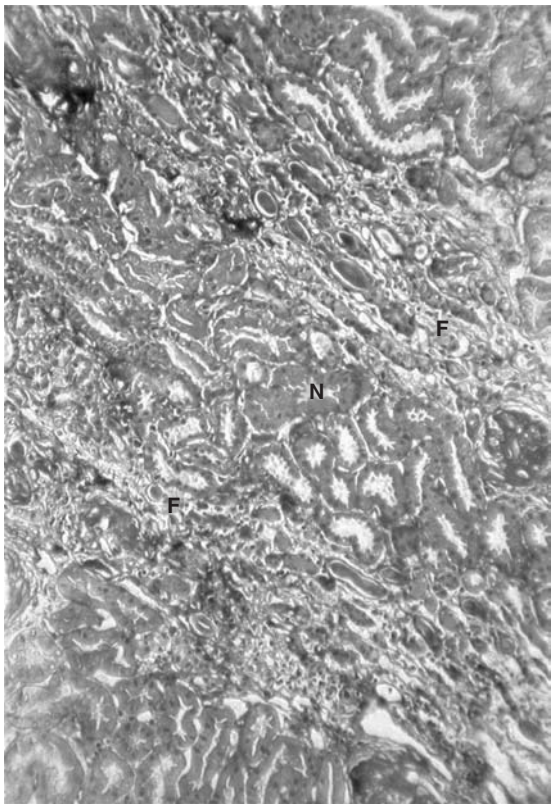


Figure 28.11 Light microscopy renal transplant biopsy showing chronic calcineurin toxicity. Alternating bands of interstitial fibrosis (F) and normally preserved tubulointerstitium (N) or 'strip fibrosis' is evident.

EBV infection after transplantation can potentially come from several sources, including donor organ, perioperative use of blood products, or subsequent community acquisition of the virus. Its incidence varies from 1 to 10% (usually close to 1%) in most series. The risk of PTLD is highest in the first year after transplantation. However, patients remain at risk indefinitely. The spectrum of clinical features include non-specific viral syndrome, weight loss, sore throat, abdominal pain, lymphadenopathy, tonsillar enlargement, hepatosplenomegaly, focal neurologic signs, and allograft dysfunction. Diagnostic evaluation of patients with suspected PTLD and treatment options are outlined in Tables 28.9 and 28.10, respectively. A positron emission tomography (PET) scan can be helpful in localizing the tumor burden of patients with PTLD (Figure 28.12). Strategies to prevent PTLD include close monitoring for EBV replication by PCR and appropriate adjustment of immunosuppressive therapies. Role of antiviral agents and IVIg infusions in preventing PTLD in children with high viral load needs formal clinical trials.

Table 28.9 Diagnostic evaluation of a patient with suspected PTLD

1. CBC with differential
2. Serum electrolytes; BUN; creatinine; liver function tests; lacatate dehydrogenase; uric acid; serum immunoglobulins
3. Chest radiograph; CT scan of chest, abdomen, and pelvis
4. Stool for occult blood
5. Biopsy of the lymph nodes and/or allograft with immunophenotyping of the cells by immunohistochemistry and flow cytometry; molecular studies for clonality; EBV demonstration in the biopsy tissue by in-situ hybridization
6. EBV viral load in blood by quantitative PCR
7. Other investigations: bone scan; bone marrow aspirate; brain CT or MRI; lumbar puncture; gastrointestinal endoscopies as indicated

Table 28.10 Treatment options for patients with PTLD

1. Reduction of immunosuppression: useful in early and polymorphic PTLD
2. Antiviral therapy with ganciclovir: unproven benefit but widely used
3. IVIg infusion: being studied currently
4. Anti B-cell antibodies such as rituximab: useful in polymorphic PTLD persisting after reduction of immunosuppression; multicentric trials in progress
5. Interferon-α: may cause severe rejection and usually not recommended
6. Chemotherapy: Burkitt's lymphoma; refractory PTLD; monomorphic PTLD; and late-onset disease
7. Surgery +/– radiation: reserved for bowel obstruction, localized lesions, or those compressing critical structures
8. Experimental therapies: autologous or HLA-matched EBV-specific cytotoxic T-cell infusions

Non-compliance in transplantation

Non-compliance, more recently named 'non-adherence', to the medical regimen is widely prevalent in children.[29,158–160] Non-adherence is seen in approximately half of the recipients of deceased organs and its prevalence increases in adolescents. It may be responsible for 25% of graft loss in children. It may vary from occasional non-adherence to complete non-adherence. Occasional non-adherence could be secondary to forgetfulness or to misunderstanding of instructions. Measuring non-adherence is difficult and crude. If caretakers admit to non-adherence, the extent is usually greater than stated. Many patients and their families will not admit to non-adherence. Pill counts or assessment of refills may be helpful in determining non-adherence. Risk factors include disorganized family structure, adolescence, and history of previous graft loss secondary to non-adherence. Non-adherence should be suspected when there are sudden fluctuations in the trough level of drugs and graft function. Parents and children should be reminded to pay special attention while traveling, around vacation times, and

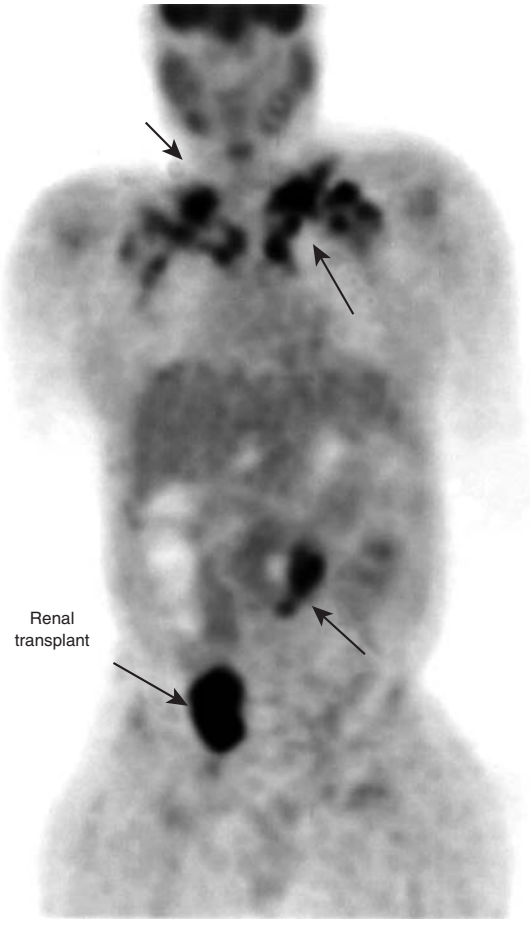


Figure 28.12 PET scan of a child with post-transplant lymphoproliferative disorder (PTLD). The patient presented with abdominal pain and a mass was detected in the para-aortic area of the abdomen. This scan shows positive pickup by the tumor mass in the abdomen as well as lymph nodes of the mediastinum and cervical region (arrows).

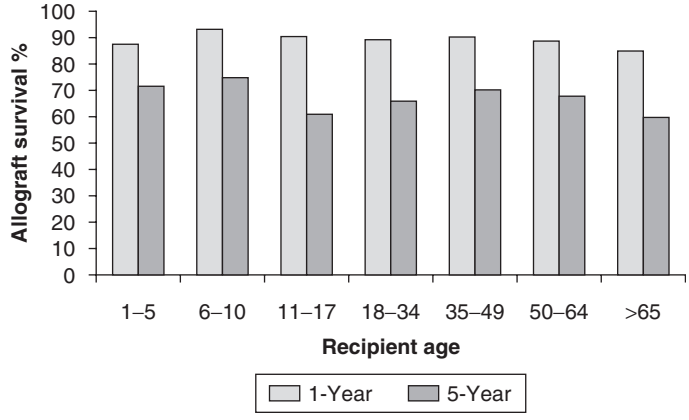


Figure 28.13 The 1- and 5-year graft survival of recipients of deceased donors. Reproduced with permission from Blackwell-synergy.[166]

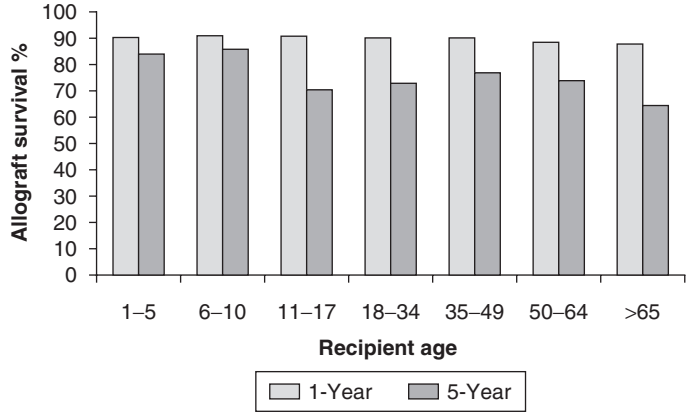


Figure 28.14 The 1- and 5-year graft survival of recipients of living donors. Reproduced with permission from Blackwell-synergy.[166]

when children first leave home to be independent. Counseling, continuing education, planning medication timings, involving children and their caretakers in decision-making processes, and frequent clinic visits are some of the strategies to improve adherence to medications.

Outcome

Renal transplantation is the most rewarding endeavor, since it transforms chronically ill children into near normal in a matter of weeks to months, with an improvement in their neurodevelopment and quality of life.[161,162] The 1- and 5-year graft survival percentages from deceased and living donors from the 2004 OPTN/SRTR annual report are shown in Figures 28.13 and 28.14, respectively.[5] As evident from the data, children younger than 10 years of age enjoy the best 5-year graft survival compared with any other age group. Unfortunately, 5-year graft survival in the 11–17 years of age group is the worst compared with the other age groups; this is probably due to a large degree of non-adherence. The benefits of transplantation come at a price of lifelong treatment with immunosuppressive medications, with concomitant side effects. The ongoing challenges include prevention and treatment of CAN; finding reliable non-invasive immune monitoring tools; decreasing the cardiovascular morbidity and mortality in the long-term survivors; dealing with the organ shortage; improving adherence, particularly in adolescents; psychosocial rehabilitation of the children and their families; and finally the elusive goal of tolerance.

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29 Nutrition in renal disease

Steven J Wassner

Maintaining adequate nutrition and normal body composition is important for patients with chronic kidney disease (CKD) as well as those with end-stage renal disease (ESRD). These needs are further enhanced in children because of the added requirements for maintaining growth. Multiple factors contribute towards poor linear growth in infants and children with CKD, including small size at birth,[1,2] poor nutritional intake,[3] electrolyte abnormalities,[3] resistance to endogenous growth hormone,[4] and alterations in the timing and intensity of the pubertal growth spurt.[5] Karlberg has convincingly demonstrated the primary role played by nutrition for growth during the first year of life.[6] Poor nutritional intake is a common concern in children with CKD, and this often leads to severe growth retardation, with many infants falling to below the 5th percentile by the end of first year of age.[7–9]

Normal nutritional requirements

Estimates of the nutritional requirements for healthy populations have been made by a variety of scientific organizations, including the World Health Organization, and the National Research Council Food and Nutrition Board, which publishes the recommended dietary allowances (RDAs). The National Research Council's recent publication lists additional standards, the Dietary Reference Intake (DRI) and Estimated Average Requirement (EAR).[10] These standards are designed for healthy individuals and for the assessment of nutritional adequacy within populations. Although needs in individual patients for a given nutrient may vary, these standards should also serve as a convenient reference for patients with CKD.

Determining adequate growth

Accurately tracking of anthropometric growth parameters is essential in monitoring growth of normal children, as well as those with CKD. Measurement of height, weight, and head circumference (infants) is a part of routine physical examinations, and methods for assessing growth are provided in standard pediatric texts. Whereas infants may change percentiles within the first 12–18 months of life, absence of growth (flattening of growth curve) should always be of concern. Infants who are below the 10th percentile of growth parameters should be carefully evaluated for treatable causes of poor growth. Other useful calculations include weight-for-height ratios, body mass index (BMI), and height velocity.[11,12] Again, infants who are at the lower percentiles of BMI need a careful evaluation. New growth charts with percentile, as well as standard deviation score (SDS) data, are now available for children in North America.[13] In assessing growth, the use of standard deviation score (SDS, or Z score) is strongly encouraged, since it is a mathematically derived numerical value that represents the trend in a particular (height, weight, or head circumference) growth parameter. SDS is calculated by using the following formula:

$$\text{SDS or Z score} = \frac{\text{Observed parameter} - \text{Mean for that parameter}}{\text{Standard deviation of the mean}}$$

Energy metabolism and requirements

Cinical experience and scientific studies have demonstrated that inadequate calorie intake is a common nutritional concern in patents with CKD. Irrespective of the underlying cause, a decrease in energy intake to less than 70% of the RDA is associated with subnormal growth.[7,9,14] With energy intakes greater than 80% of the RDA for height age, there is no correlation between energy intake and linear growth.[7,9,14] Whereas macronutrient requirements are unaltered in CKD,[15] spontaneous intake of food (energy) is low in both animals and humans with CKD and ESRD.[8,16–19] Energy supplements have been demonstrated to be effective in improving growth rates in the youngest children with CKD and ESRD, but are much less effective in older children.[7,9,15] It is important, however, to note that overfeeding can lead to obesity without significant improvement in linear growth. With rare exceptions, the nutritional goal should be for a total energy intake of approximately 100–110% of the RDA, adjusted for height age (Table 29.1).

Table 29.1 Recommended energy and protein intakes in children by age

	Predialysis		Hemodialysis		Peritoneal dialysis			
	Energy[a]	Protein[b]	Energy[a]	Protein[b,c]	Energy[a,d]	Protein[be]	Calcium[f]	Phosphorus[f]
0–6 months	100–110	2.2	100–110	2.6	100–110	3	400	300
6–12 months	95–105	1.5	95–105	2	95–105	2.4	600	500
1–3 years	90	1.1	90	1.6	90	2.0	800	800
4–10 years	70	0.95	70	1.6	70	1.8–2.0	800	800
11–14 years (boys)	55	0.95	55	1.4	55	1.8	1200	1200
11–14 years (girls)	47	0.95	47	1.4	47	1.8	1200	1200
15–18 years (boys)	45	0.85	45	1.3	45	1.5	1200	1200
15–18 years (girls)	40	0.85	40	1.2	40	1.5	1200	1200

[a]Energy in kcal/kg/day.
[b]Protein in g/kg/day.
[c]Protein intakes increased by approximately 0.4 g/kg/day to account for hemodialysis losses.
[d]Note that up to 10% of the total caloric intake (10 kcal/kg/day) can be absorbed as dextrose via the dialysate. Obesity may become a concern for some children and adolescents on peritoneal dialysis.
[e]Protein requirements on peritoneal dialysis reflect the significant loss of proteins through the dialysis fluid.
[f]Phosphorus in mg/day.
Adapted from References 3, 10, and 56.

Protein metabolism and requirements

Infants and children with CKD have an altered body protein mass and demonstrate abnormalities in protein metabolism. Subnormal lean body mass, low serum albumin and prealbumin concentrations, and abnormal intracellular and extracellular amino acid concentrations have all been reported in CKD.[20]

Healthy children in North America eat approximately 150% of the RDA for protein. Even when energy intake decreases to as low 70%, it is likely that protein intake remains relatively normal in these children. Therefore, lack of dietary protein may be less of a contributor for growth failure for children with CKD and ESRD in North America, except when associated with clinical states of high protein loss, such as nephrotic syndrome or peritoneal dialysis. High protein diets are avoided in CKD and ESRD in order to limit excessive urea and acid production. In addition, phosphorus intake, which correlates highly with protein intake, can result in hypocalcemia, hyperparathyroidism, and the development of renal osteodystrophy. Finally, at least in rats,[21] high protein intakes clearly accelerate the decline in glomerular filtration rate (GFR).[22] Changes in plasma and intracellular amino acid concentrations are only partially amenable to therapy.

For reasons noted above, some have suggested the use of a low-protein diet (below the RDA standards) for management and preserving renal function in patients with CKD. Studies in adults using such low-protein diets have been equivocal.[23,24] However, meta-analysis of several studies in adults has supported the role of such a dietary intervention in the management of CKD.[25] One of the reasons for the failure of studies to be conclusive in their recommendations of protein-restricted regimens is that adherence to low-protein diets was poor, and most patients ate significantly more protein than prescribed.[23,26] A randomized study in children demonstrated no beneficial effect of protein limitation.[26] Severe protein restriction may have an adverse impact on growth in infants[27], as has been demonstrated in a preliminary study. Therefore, it is generally recommended that protein intake in children with CKD should be at the RDA for height age (see Table 29.1).

Lipid metabolism

Individuals with CKD demonstrate significant abnormalities in lipid and lipoprotein metabolism. Those with nephrotic-range proteinuria have hyperlipoproteinemia and hypercholesterolemia, which can be severe. Even for those without significant proteinuria, hypertriglyceridemia and hypercholesterolemia, which are associated with decreased concentrations of high-density lipoprotein (HDL) cholesterol, are often present early in the course of CKD and continue through both dialysis and transplantation.[28–30] In adults, premature coronary artery disease is a major cause of mortality in both the dialysis and transplant populations. Available evidence suggests that this process is already present in adolescents with CKD and ESRD.[31,32]

In animal studies, lowering dietary fat content delays progression to ESRD, but the evidence in humans is equivocal.[3] In addition, benefits of dietary fat restriction in children must be balanced by the importance of fat as a high-density energy source and its role in increasing flavor and palatability of diet.

Use of mono- and polyunsaturated fats in diet, as opposed to saturated fats, should be encouraged.

Fluid and electrolytes

The normal kidney has an immense ability to adapt to a wide range of fluid and electrolyte intake. As CKD progresses, the renal capacity for control of electrolyte and fluid balance is compromised. Development of volume overload or hypertension in patients signals the need to limit sodium intake. On the other hand, CKD in children with renal dysplasia, or obstructive uropathy and tubulointerstitial disorders are generally associated with renal sodium wasting. Sodium supplementation is commonly necessary in such patients to maintain normonatremia.

It is generally not necessary to limit water intake in most children with CKD, since their thirst mechanisms are well preserved, and they can drink to isotonicity. Infants with high urine output associated CKD may need to be provided with additional water in order to prevent dehydration. In contrast, fluid restriction may be necessary in those with CKD or ESRD and associated oliguria.

The kidney has a remarkable ability to excrete potassium, but as renal function declines, it is reasonable to limit intake of foods with high potassium content. Hyperkalemia presenting in individuals with moderate CKD generally indicates an acute potassium overload (e.g. dietary indiscretion, intravenous administration), a significant catabolic event, or dehydration.

Metabolic acidosis may be seen in children with GFR levels as high as 50 ml/min/1.73 m^2.[33] Acid production results from the metabolism of amino acids, in an amount proportional to dietary protein intake. Older children and adults generate approximately 1–2 millimoles of acid per kilogram body weight per day. In rapidly growing children, an additional source of acid production involves the calcification of osteoid, which releases hydrogen ions in exchange for calcium. Thus, acid production during rapid growth periods may be as high as 4–5 millimoles per kilogram body weight per day. As renal function declines and renal ammonia production diminishes and metabolic acidosis ensues.

The development of metabolic acidosis has multiple metabolic impacts, including decreased secretion of growth hormone, limitation of statural growth, increase in the rate of protein catabolism, and decreased rate of bone calcification.[34–38] It is important to limit excessive protein intake and provide bicarbonate or citrate solutions in order to keep serum bicarbonate levels within the normal range.

Fat-soluble vitamins

With the exception of vitamin D, there is no evidence to indicate that the metabolism of fat-soluble vitamins is abnormal in CKD, and supplementation is not necessary. Vitamin A supplements should be specifically avoided, as vitamin A can accumulate in children with CKD, resulting in vitamin A toxicity.[39] Vitamin E supplements have been suggested as a therapy in specific forms of glomerulonephritis but are not necessary as a standard nutritional supplement. Carnitine, a transporter of fatty acids, may be deficient in CKD and has been suggested as an etiology of hyperlipidemia.[39a] Evidence to support this claim is limited and routine supplementation is not currently recommended.

Water-soluble vitamins

Supplements of the water-soluble vitamins are routinely provided to patients with CKD and ESRD. Excessive amounts of vitamin C can lead to increased serum oxalate concentrations. Particular attention should be paid to folate, which, unless supplemented, can limit the effectiveness of administered erythropoietin. Hyperhomocysteinemia has been shown to be an independent predictor of heart disease. Although supplementation with vitamin B_6, folate, and vitamin B_{12} improves homocysteine concentrations in patients with normal renal function and those post-transplantation, there is no consensus on their efficacy in other individuals with CKD.[40]

Minerals

Calcium and phosphorus metabolisms are altered in all individuals with significant CKD, and are intimately involved with alterations in both parathyroid function and vitamin D metabolism. From a nutritional point of view, the main concerns relate to a decreased calcium intake/uptake, via the gastrointestinal tract, and insufficient renal phosphorus excretion. Average Western diets contain significantly more phosphate than is required, and its intake must be modified in CKD and ESRD by limiting meat and dairy products. For almost all patients, appropriate control of serum phosphate concentrations also requires the addition of phosphate binders, which form insoluble products and prevent phosphate absorption from the gastrointestinal tract. Most commonly used phosphate binders contain calcium, thus providing additional calcium intake. Sevelamer hydrochloride (a calcium-free phosphate-binding agent) may be used in patients with concerns for hypercalcemia. Historically, aluminum compounds were also used as phosphate binders, but their use is strongly discouraged, since aluminum buildup is associated with significant neurodevelopmental and bone abnormalities.[41,42] Serum phosphate levels should be adjusted to age-appropriate normals, which are significantly higher in infants than in older children and adults. Infants receiving low-phosphate formulas can develop hypophosphatemia, and poor bone mineralization. Recommended calcium and phosphorus intakes at different ages are given in Table 29.1.

Iron deficiency can be a limiting factor for erythropoiesis, and iron supplements are necessary for patients receiving

erythropoietin. Oral iron supplementation should be considered for patients with CKD or those on peritoneal dialysis. Intravenous iron may be necessary for circumstances where severe iron deficiency is a clinical concern, oral iron therapy is ineffective, or in patients who do not tolerate oral iron therapy. There are no data to suggest that trace elements need to be supplemented in CKD or in those on dialysis.

Nutrition in special circumstances

Protein-losing states

Children with nephrotic syndrome lose significant amounts of protein due to renal tubular catabolism and urinary excretion. Oral protein supplements are unable to remedy the hypoalbuminemia, and experimental evidence suggests that higher protein intake actually increases urinary protein excretion and lowers serum albumin concentrations.[43] There are no scientific studies that address the optimal oral or enteral intake for patients with nephrotic syndrome. Patients with congenital nephrotic syndrome have high urinary protein losses and become protein depleted, even with a normal GFR. Nutritional care in this group of infants requires enteral feeds and repeated albumin infusions to prevent severe hypoproteinemia and edema formation. As these children progress to renal failure and undergo bilateral nephrectomy, nutritional rehabilitation prior to renal transplantation is necessary.[44,45]

Tubular dysfunction

Developmental anomalies are the primary cause of CKD in infants, and renal tubular dysfunction plays a prominent part in their clinical manifestations. Even at a relatively normal GFR, these patients may have both proximal and distal tubular defects, and may be unable to conserve sodium and bicarbonate, fail to excrete sufficient potassium, or concentrate urine effectively.

Inability to conserve sodium (and chloride) leads to intravascular volume depletion, with elevated urea and creatinine concentrations. In response to intravascular volume depletion, proximal bicarbonate reabsorption is enhanced, resulting in a relatively preserved serum bicarbonate level. Without adequate distal sodium delivery, potassium excretion is impaired, with resultant hyperkalemia. Institution of salt and water supplementation with restoration of intravascular volume often results in the correction of hyperkalemia, metabolic acidosis, and elevated blood urea nitrogen (BUN) and creatinine concentration. These infants often require a volume intake as high as 200 ml/kg/day, coupled with a sodium intake of 6–8 mEq/kg/day. Some infants may manifest hyporeninemic hypoaldosteronism, and require mineralocorticoid supplementation to prevent significant hyperkalemia.[46–48]

Infants and children with tubular disorders may have chronic intravascular volume depletion and dehydration, which is difficult to recognize clinically. In the absence of contraindications, such as hypertension or clinical volume overload, salt intake should be liberalized in these patients. Since infants drink to caloric satiety, it is frequently necessary to dilute (not concentrate) the infant's formula to increase volume intake.

Enteral feeding

Deficient oral intake impedes adequate nutrition and hinders growth in infants and children. Enteral nutritional supplementation using a nasogastric, nasojejunal, or gastrostomy route should be instituted in patients unwilling or unable to take prescribed nutrition and needed sodium and water supplementation orally. It is important to prepare parents for this possibility early in the course of care of CKD. The use of enteral feeds is often accompanied by significant dietary modifications, as palatability no longer remains an issue. All combinations of oral intake, bolus as well as enteral continuous feeding schedules, have been utilized with good results. Infants with CKD demonstrate a high incidence of gastroesophageal reflux, and surgical antireflux procedures may be necessary. Interestingly, there is poor correlation between the degree of regurgitation, or emesis, and growth rates.[49] Feeding team and clinic personnel should be utilized to address nutritional aspects in patients with CKD, since a significant number of these infants require assistance in relearning feeding skills.

Available nutritional supplements

In order to achieve adequate energy and protein intake in infants and toddlers with CKD, it is often necessary to provide nutritional supplements. This is generally achieved by changing to a formula containing higher energy or protein concentrations (Table 29.2). Another approach, particularly useful for younger infants, involves supplementing either oral or enteral feeds with additional energy or protein. Energy may be supplemented using complex glucose polymers or as a lipid. Protein supplements are available in powder form (Table 29.3).

Acute renal failure and intravenous hyperalimentation

The primary nutritional aim in acute renal failure (ARF) is to provide sufficient energy and protein intake to promote renal tissue healing and restore body composition. These patients are more likely to be recuperating from trauma or surgery and to have multiple organ dysfunction. They are often immobile, maintained on respirators, and may be febrile, septic, or be recovering from surgery, all of which result in a catabolic state. It is often difficult to estimate actual nutritional requirements in such patients and large fluid volumes are often necessary for parenteral nutritional therapy in such patients. Unfortunately,

Table 29.2 Nutritional composition of human milk and commercially available nutritional supplements meant for use in infants with kidney disease

	Values per 100 ml formula										
	Energy (kcal/oz)	Energy (kcal)	Protein (g)	Carbohydrate	Fat	Na (mEq)	K (mEq)	Ca (mg)	P (mg)	Mg (mg)	Osmolality (mOsm/kg H_2O)
Human milk	20	68	0.9	7.2	3.9	0.8	1.4	35.0	15.0	4.0	290
Sim PM 60/40	20	68	1.6	6.9	3.8	0.7	1.5	38.0	19.0	4.1	280
LactoFree	20	68	1.5	6.9	3.7	0.8	1.8	54.6	36.7	5.3	200
Pregestimil	20	68	1.9	6.9	3.8	1.1	1.9	63.6	42.6	7.3	320
Pediasure	30	100	3.0	11.0	5.0	1.7	3.4	97.0	80.0	19.8	310
Nutren Jr.	30	100	3.0	12.8	4.2	2.0	3.4	100.0	80.0	20.0	350
Infants with acute renal failure or need for careful electrolyte balance											
RenalCal[a]	60	200	3.4	29.0	8.2	0.2	0.2	5.8	0.0	0.0	600
Predialysis											
Suplena	60	200	3.0	25.5	9.6	3.4	2.9	138.5	72.8	21.5	600
Dialysis											
Nepro	60	200	7.0	21.5	9.6	3.6	2.7	137.3	68.6	21.5	665
Novasource Renal	60	200	7.0	20.0	10.0	pack 3.9/ closed system 7.0	pack 2.1/ closed system 2.8	130.0	65.0	20.0	700
Nutrirenal	60	200	7.0	20.5	10.4	3.2	3.2	140.0	70.0	20.0	650

[a]Acute renal failure or short-term use only. No fat-soluble vitamins, negligible electrolytes.

Table 29.3 Dietary supplements for infants and children with chronic kidney disease (CKD) and end-stage renal disease (ESRD)

Product	Type	Form	Energy content	Protein	Fat	Percent water
Enfamil Human Milk Fortifier (Mead Johnson Nutritionals)	Multiple	Powder	1 packet = 2 kcal/oz	1 packet = 0.28 g	1 packet = 0.25 g	
Polycose (Ross Laboratories)	Energy	Powder	8 kcal/level teaspoon			
Polycose (Ross Laboratories)	Energy	Liquid	2 kcal/ml			70
MicroLipid (Novartis Medical Health)	Energy	Liquid	4.5 kcal/ml		5.1 g/100 ml	45
ProMod (Ross Laboratories)	Protein	Powder	28 kcal/level teaspoon	5 g/level teaspoon	0.6 g/level teaspoon	

no specific nutritional formulations have been developed that can accelerate recovery from acute renal failure.

The specific challenge in patients with ARF is meeting their nutritional needs within the constraints of a limited fluid volume intake. Even at the highest concentrations of glucose, amino acids, and lipid in the intravenous hyperalimentation, it is nearly impossible to meet maintenance requirements, unless some form of dialysis therapy, or continuous renal replacement therapy (CRRT), is instituted.

Whenever possible, enteral feedings should be utilized. They are more physiologic and (with current formulations) it may be possible to achieve a higher caloric density using enteral as

opposed to intravenous alimentation. Provision of sufficient energy is paramount in order to prevent endogenous protein catabolism. Protein requirements should be met by providing a balanced intravenous amino acid solution in an amount to cover RDA for age. There is little evidence to suggest that providing additional protein improves protein anabolism, but urea generation rates increase with increased protein intake.[50] Intravenous lipids can provide significant caloric intake (20% Intralipid contains 2 kcal/ml solution and only 80% of the total volume is water). It is important to assess actual caloric requirements, as providing excess glucose can lead to excessive CO_2 production, which may delay extubation.[50]

Nutrition in chronic dialysis patients

Hemodialysis

Small amounts of glucose and amino acids are removed during a routine hemodialysis session. In addition, small, but significant, amounts of red blood cell loss during hemodialysis leads to iron depletion. Whereas dialysis itself has been considered a catabolic event, individuals eating nutritionally balanced diets have no specific additional requirements for protein or amino acids. Children on hemodialysis should be prescribed diets containing the RDA for energy. The current recommendations for protein intake reflecting a consensus view[51] are listed in Table 29.1.

Peritoneal dialysis

From studies utilizing both dietary recall and from direct measurement of urea nitrogen appearance rates, it was found that the majority of children on peritoneal dialysis receive less than the recommended protein intakes.[52–54]

A recent dialysis network survey demonstrated that approximately 15% of pediatric peritoneal dialysis patients had a serum albumin of less than 2.9 g/dl.[53] In contrast, depending upon the dialysate glucose concentration used for therapy, these patients absorb upwards of 10 kcal/kg/day through the peritoneal membrane, while losing proteins (primarily albumin) into the dialysate.[55] Daily loss of albumin in peritoneal dialysis can be similar in magnitude to a patient with nephrotic syndrome, with losses exceeding 3 g/day.

Monitoring of nutrition on dialysis

Anthropometric data trends (weight, height, skin-fold thickness) provide an overall measure of nutritional adequacy. Laboratory data that can be helpful in providing additional monitoring of nutrition should include serum albumin and predialysis BUN. A declining level in both of these parameters is indicative of malnutrition. All hemodialysis units monitor dialysis efficiency, and those utilizing Kt/V calculations can also derive protein catabolic rates (PCR), with low rates suggesting insufficient protein intakes. PCR of less than 1 g/kg/day is indicative of protein malnutrition and should lead to institution of corrective steps. Infusion of amino acid solutions during hemodialysis has been reported to result in short-term improvements in protein metabolism.[54] However, costs associated with such a therapy are significant and limit a wider use of this therapy.

Concluding remarks

The association between CKD, malnutrition, and decreased growth has been recognized for at least three decades, and much effort has gone into both the description of the problem and its therapy. Careful attention to nutritional needs can result in an improvement in growth of children with CKD to within 1 SDS below normal for height. Use of recombinant growth hormone can further improve growth rates. Maintaining adequate nutrition in infants and children with CKD is challenging and requires the combined efforts of patients and their families, as well as a dedicated team of professionals with specialized training in pediatric perspectives of nutrition.

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Part VI

Hypertension

30 Hypertension: Epidemiology and evaluation

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Cardiovascular diseases, including myocardial infarction and stroke, represent the leading causes of death in the United States, and currently account for more than US$390 billion in direct and indirect healthcare cost annually.[1] Although hypertension has been a well-documented risk factor for these outcomes in adults for a number of years, it has only been over the last two decades that the body of knowledge about childhood hypertension has grown significantly. It is now clear that the precursors for adult cardiovascular disease begin in childhood and that hypertension should no longer be considered an adult disease. This chapter provides an overview of the epidemiology and pathophysiology of childhood hypertension as well as a clinical discussion concerning its etiology, detection, and diagnostic evaluation.

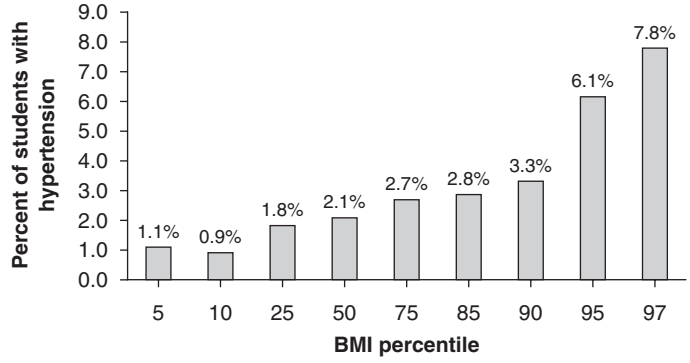

Figure 30.1 Prevalence of hypertension by body mass index (BMI) percentile after three screenings in 17 850 adolescents in the Houston area public schools (authors' unpublished data).

Epidemiology

The prevalence and distribution of hypertension among children is difficult to characterize because of the great variability between studies in definitions and blood pressure (BP) measurement techniques, which have only been well-standardized since the second task force report in 1987.[2] Coupled with this are the changing cardiovascular disease risk factors among children in the United States. Currently, approximately 15% of children between the ages of 6 and 19 are overweight, as compared to an estimated 5% 30 years ago.[3] Because the prevalence of hypertension is known to increase with increasing body mass index (BMI; Figure 30.1), it is likely that more recent studies that cite the prevalence of hypertension among adolescents to be near 5%[4] are closer to reality than the traditional estimate of 1% based on older studies.[2,5] Along with this increase in prevalence has come a shift in prevailing diagnoses from those associated with secondary causes to essential hypertension, especially among adolescents.

Definition of hypertension

BP values used to define hypertension in adults are based on analysis of an increased morbidity and mortality related to these higher pressures.[6] Because these adverse events do not typically occur in younger populations, the definition for childhood hypertension is based on normative data for BP patterns in healthy children. As children grow, their BP also increases gradually. Normative values of BP are now based on gender, height, and age of children (Tables 30.1 and 30.2).[7] BP readings below the 90th percentile for age, gender, and height percentile are considered normal. Children with either systolic or diastolic BP falling between the 90th and 95th percentiles are regarded as prehypertensive. However, adolescents whose BP measures above 120/80 mmHg should be considered prehypertensive as well, regardless of their 90th percentile. The recognition of prehypertension is important because of the potential to intervene to

Table 30.1 Blood pressure (BP) levels for boys by age and height percentile

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Percentile of height							Percentile of height						
Age (year)	BP percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90

Table 30.1 (Continued)

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Percentile of height							Percentile of height						
Age (year)	BP percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Reproduced from Reference 7.

prevent the development of true hypertension. In adults, the relationship between BP and the risk of cardiovascular disease is continuous and independent of other risk factors. This risk begins at the BP of 115/75 mmHg, a value below the definition for prehypertension, and the risk doubles with each increment of 20/10 mmHg.[8]

Children whose BP falls above the 95th percentile have true hypertension. Current recommendations are that hypertension in children be staged in order to better assess the need for more immediate and in-depth evaluations.[7] Patients with BP values between the 95th percentile and the 99th percentile + 5 mmHg are classified as stage 1. Those falling above the 99th percentile + 5 mmHg have stage 2 hypertension, and therefore warrant more rapid intervention (Table 30.3).

Unless a patient has severe and/or symptomatic hypertension, high values must be confirmed on three separate occasions. Occasionally, patients have consistently elevated BPs (>95th percentile) in the physician's office but BP is normal (<90th percentile) at home or in the patient's regular environment. This is termed 'white coat hypertension,' and 24-hour ambulatory BP monitoring is the best way to establish the diagnosis of this condition. The significance of white coat hypertension in children has yet to be determined, although the risk for cardiovascular disease is less than true hypertension in adults.[9]

Pathophysiology

It is often useful to consider the pathophysiology of hypertension according to its determinants: cardiac output and peripheral vascular resistance (Table 30.4). Therefore, clinical disorders that increase either cardiac output or peripheral vascular resistance also raise BP. While either can increase independently through a number of different mechanisms, they also have a dependent interaction between themselves. For

Table 30.2 Blood pressure (BP) levels for girls by age and height percentile

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Percentile of height							Percentile of height						
Age (year)	BP percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	114	115	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89

Table 30.2 (Continued)

		Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Percentile of height							Percentile of height						
Age (year)	BP percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Reproduced from Reference 7.

example, if the initiating event causes a rise in cardiac output, a compensatory rise in peripheral vascular resistance develops over time. Even if the inciting event resolves and cardiac output returns to normal, BP may remain elevated due to the consistently elevated peripheral vascular resistance.

Cardiac output is determined by stroke volume and heart rate, although most mechanisms of persistent hypertension are associated with an increased stroke volume and only slight increases in heart rate. Despite this observation, mounting evidence over the last decade has shown that elevated heart rate has an important prognostic significance for cardiovascular disease.[10] Increased stroke volume is usually caused by an increased intravascular volume, either from excessive fluid retention, or from fluid shifts into the vascular space.[11,12] Salt retention is a major contributor to increased intravascular fluid and may result from either excessive intake, or increased renal tubular resorption of sodium, as is seen with activation of the renin–angiotensin–aldosterone system (Figure 30.2) and hyperinsulinemia.[13,14] Increased sympathetic tone increases cardiac output by stimulating renin release, as well as by increasing cardiac contractility and heart rate.

Changes in peripheral vascular resistance result from either functional or structural abnormalities. Increased angiotensin II, elevated sympathetic activity, increased endothelins (prostaglandin H_2; PGH_2), decreased endothelial relaxation factors (e.g. nitric oxide), and genetic abnormalities in vascular cell receptors are all associated with increased vascular smooth muscle contractility, and thus raise peripheral vascular resistance.[15] It has also been recently suggested that uric acid, which is known to be elevated in hypertensive children, may play a role in the pathogenesis of renal arteriolar changes seen in essential hypertension.[16–18] Chronically, these changes in vascular compliance and associated inflammation lead to endothelial dysfunction and vascular remodeling – a state that may be reversible in some.[19] Often, however, this state progresses to intimal fibrosis and atherosclerosis, which is less likely to be

Table 30.3 Classification of blood pressure (BP) in children and adults

	Pediatric definition	Adult definition
Normal	<90th percentile	<120/80
Prehypertensive	90th to <95th percentile, or if BP exceeds 120/80 even if <90th percentile up to <95th percentile[a]	120–139/80–89
Stage 1 hypertension	95th to 99th percentile + 5 mmHg	140–159/90–99
Stage 2 hypertension	>99th percentile + 5 mmHg	≥160/100

[a]This occurs typically at 12 years old for systolic blood pressure (SBP) and at 16 years old for diastolic blood pressure (DBP).

Table 30.4 Pathophysiology of hypertension

Increased cardiac output	Increased peripheral vascular resistance
Increased intravascular volume ↑ Salt intake ↑ Renal sodium resorption ↑ Increased renin/aldosterone ↑ Insulin ↑ Sympathetic tone	Increased vascular contractility: ↑ Angiotensin II ↑ Sympathetic activity ↑ Endothelin (PGH_2) ↓ Endothelial relaxation factors (NO)
Increased contractility: ↑ Sympathetic tone	Structural changes: Endothelial dysfunction Intimal fibrosis Atherosclerosis
Blood Pressure = Cardiac output × Total peripheral vascular resistance Cardiac output = Stroke volume × Heart rate	

PGH_2, prostaglandin H_2; NO, nitric oxide.

remediable. How the interaction of all of these factors ultimately leads to long-standing hypertension is complex, and has yet to be completely understood, especially for essential hypertension.

Measurement of blood pressure

Proper measurement of BP is critical for diagnosising of hypertension. Incorrect measurements may be obtained from errors related to the patient, equipment, or the observer. To obtain an accurate BP, the patient should be resting for at least 5 minutes in a comfortable seated position, with back supported and feet firmly on the floor.[20,21] In infants and young children, BP may be measured with the patient supported in a caregiver's lap, or lying down.[22] Regardless, readings should always be taken in the upper arm, with an appropriate size cuff and the arm resting at heart level. Currently published normal values are based on casual arm BP measurements. Because readings obtained in the leg may be 10–20 mmHg higher than the arm pressures in any given individual, hypertension should not be diagnosed with leg pressures. The BP cuff should be chosen based on the size of the child's arm and size of the bladder in the cuff. Commercial standards are not uniform, and cuff labeling is not always appropriate (e.g. not all 10 year olds should have their BP measured with the 'child cuff').

Conventionally, the BP cuff should have a bladder width that is at least 40% of the mid-arm circumference (point midway between the olecranon and the acromion) and bladder length covering at least 80% of the circumference of the arm without overlapping.[7] Using too small a cuff can produce erroneously high BP values, whereas too large a cuff may generate results slightly lower than the patient's actual BP. A larger cuff size should be chosen for patients whose mid-arm circumference measures just above the smaller cuff size, even if the cuff seems too large.

A number of techniques for measuring BP non-invasively are available. The gold standard is auscultatory measurement using a mercury manometer.[23] However, these are becoming less available due to environmental concerns of mercury exposure. Aneroid manometers for use in similar auscultatory measurements are also available. Although these instruments have been shown to be accurate, improper maintenance and lack of routine calibration may lead to incorrect readings.[24,25] Either technique requires the observer to document Korotkoff sounds heard over the brachial artery using the bell of a stethoscope while deflating the BP cuff. Systolic BP is recorded at K1 (Korotkoff phase 1) – the onset of sound. This may be followed by a long pause (termed the auscultatory gap) before sounds begin a rhythmic tapping. Diastolic BP is defined at K5 – the point at which sound disappears completely. Although K4 (muffling of sounds) is no longer recommended to define diastolic BP, it may be the only option in young children in whom K5 is close to zero.[7]

Oscillometric techniques utilized by most automated BP devices were designed to increase ease of measuring BP, while decreasing the probability of observer error and bias. Rather than determining Korotkoff sounds, these instruments measure the amplitude of oscillation generated by the artery wall as the

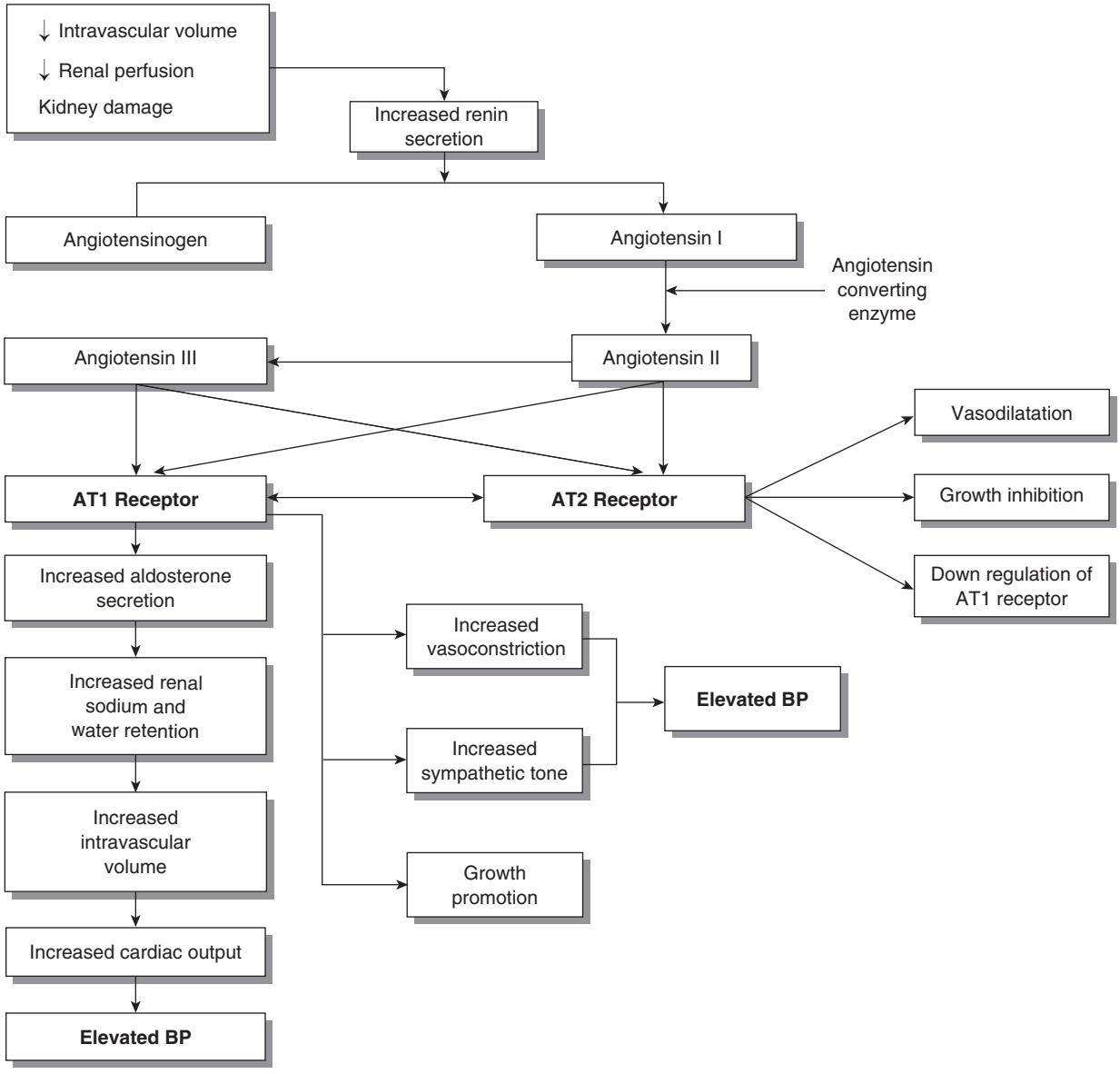

Figure 30.2 Renin–angiotension–aldosterone system in blood pressure regulation.

BP cuff is deflated. The amplitude reaches its peak near the mean arterial pressure. Proprietary calculations, which vary between manufacturers, are then used to calculate the systolic and diastolic BPs from this measured mean arterial pressure.[26] Whereas these measurements are similar to those obtained with auscultatory techniques, the systolic BP does tend to be slightly higher, particularly on the first reading.[27,28] For this reason, some experts recommend taking multiple BPs and discarding the first. Whichever technique is utilized, it is important that all equipment is routinely serviced according to the manufacturer's suggestions to minimize equipment error when diagnosing hypertension.

Clinical manifestations

The majority of patients with essential hypertension are identified at a routine school physical or during a physician's visit for another complaint. Most of these patients are asymptomatic, but some may complain of headaches, dizziness, fatigue, or other mild cardiovascular symptoms. Patients with secondary causes frequently present with symptoms related to the underlying disease (e.g. hematuria with glomerulonephritis or hot flashes and weight loss with hyperthyroidism), rather than symptoms of high BP.

Hypertensive encephalopathy and emergencies

Although less common, severe hypertension can present with life-threatening symptoms. Hypertensive emergency is defined as presentation of a patient with a critically elevated BP and evidence of life-threatening end-organ damage. Children with hypertensive emergencies most frequently present with neurologic symptoms, although heart failure and renal insufficiency have also been reported. Hypertensive emergencies are more often seen in secondary forms of hypertension, and its reported prevalence varies widely from 20–50% of patients with renovascular hypertension.[29,30]

Hypertensive encephalopathy typically manifests as a headache with changes in mental status and seizures. Other reported symptoms include facial palsy (particularly Bell's palsy),[31,32] visual changes which may lead to blindness,[33,34] and coma. The pathophysiology behind this disorder involves a disruption in the normal autoregulatory mechanisms of cerebral blood flow.[35] With severe and abrupt increases in blood pressure, the cerebral vasculature is unable to constrict appropriately to maintain constant cerebral blood flow. This leads to cerebral hyperperfusion and resultant edema, most commonly manifesting as posterior leukoencephalopathy affecting the parieto-occipital white matter (Figure 30.3).[36,37] With a slow chronic elevation in BP, the cerebral autoregulatory mechanisms are able to sufficiently adapt.[38] Therefore, hypertensive encephalopathy is rarely seen in patients with chronic hypertension but is commonly seen in patients developing a sudden rise in BP, such as children with acute glomerulonephritis.

The reported outcome of patients suffering from hypertensive emergencies has varied considerably. In one early series of children with hypertensive encephalopathy, 6 of 11 patients had long-term neurologic deficits, and 1 patient died during the hypertensive crisis.[39] However, in another series of 45 patients with a single episode of hypertensive encephalopathy, no permanent neurological sequelae were observed.[40] Management of these patients may account for the variation that has been seen among reported series. To compare different treatment strategies, Deal et al report the outcomes of 110 severely hypertensive pediatric patients over a 10-year period.[33] The initial 57 patients were treated using bolus medications with the intent to normalize blood pressure in 12–24 hours. Of these, 13 patients (23%) developed significant complications, including acute renal failure, both transient and permanent visual loss, and transverse ischemic myelopathy. Subsequently, continuous infusions were used to treat 53 patients, with a goal of gradual BP reduction over 96 hours. Only 2 patients (4%) developed transient acute renal failure and no neurologic complications were observed.

Patients presenting with hypertensive emergency or urgency (severely elevated BP) require immediate intervention and evaluation. However, in both instances, care should be taken not to lower BP too rapidly, which can result in complications of cerebral hypoperfusion, such as ischemic neuropathy of the optic nerve, transverse ischemic myelopathy, and renal impairment.[41–45]

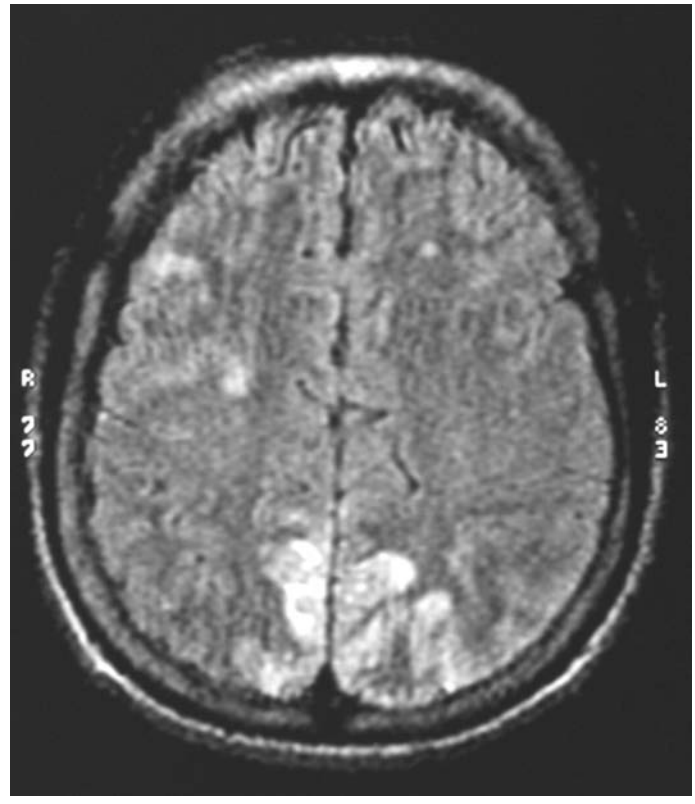

Figure 30.3 MRI of brain of an adolescent patient with hypertensive encephalopathy. Occipital area shows increased signal suggestive of edema (white area).

Etiology of hypertension in children

Hypertension may be either primary (essential), or secondary to another underlying medical condition. Generally, the majority of cases of childhood hypertension are considered to be secondary. However, the number of children with essential hypertension is on the rise. Despite this trend, it is important that practitioners continue to investigate the secondary causes, particularly among the very young and severely hypertensive.

Secondary hypertension

Renal parenchymal diseases

The most common causes of secondary hypertension are due to underlying kidney disease. Renal parenchymal damage from vesicoureteral reflux, with or without recurrent urinary tract infections and obstructive uropathy, constitutes 30–40% of children with sustained secondary hypertension seen in tertiary care referral centers. Chronic glomerulonephritis is also relatively common, affecting 23–28% of this population.[46]

Although representing a smaller number of total patients, most other renal diseases (Table 30.5) can be associated with hypertension. In fact, many of these patients, especially those with end-stage renal disease (ESRD), become the most difficult to manage.

Renovascular diseases

Renovascular causes of hypertension are important to recognize, because of their potential for surgical cure. Renal artery stenosis is found in 8–10% of hypertensive children referred to tertiary centers.[47,48] Unilateral fibromuscular dysplasia of the renal

Table 30.5 Causes of hypertension in children and adolescents

Transient hypertension	Sustained hypertension
Error in BP reading	Essential hypertension
Renal diseases: • Hemolytic uremic syndrome • Acute poststreptococcal glomerulonephritis • Acute tubulointerstitial nephritis • Rapidly progressive glomerulonephritis • Henoch–Schönlein purpura nephritis • Relapse of nephritis associated with systemic disease (lupus, other vasculitis) • Nephrotic syndrome (if hypervolemic) • Acute obstruction • Acute tubular necrosis • Renal trauma	Renal diseases: • Chronic pyelonephritis and reflux nephropathy • Chronic glomerulonephritides • Chronic renal failure • Hemolytic uremic syndrome • Polyarteritis nodosa, systemic vasculitis • Congenital renal anomalies (dysplasia) • Inherited parenchymal disease (ADPKD, ARPKD)
Vascular disorders: • Renal artery compression (abdominal compartment syndrome) • Renal vein/artery thrombosis • Arteriovenous fistulae • Trauma	Vascular disorders: • Coarctation of the aorta • Renal artery stenosis (fibromuscular dysplasia, congenital) • Renal artery thrombosis and embolization • Neurofibromatosis • Renal transplant arterial stenosis
Neurologic causes: • Seizures • Increased intracranial pressure (tumor, hydrocephalus) • Guillain–Barré syndrome • Poliomyelitis • Spinal cord injury • Dysautonomia	Endocrine disorders: • Congenital adrenal hyperplasia: 11β-hydroxylase deficiency 17α-hydroxylase deficiency • Conn's syndrome • Cushing disease and syndrome • Hyperthyroidism
Drug-induced hypertension: • Corticosteroids • NSAIDs • Oral contraceptive agents • Erythropoietin • Sympathomimetic drugs, nasal decongestants (pseudoephedrine) • Street drugs (cocaine, amphetamines)	Renal tumors: • Wilms' tumor • Hamartomas • Hemangiopericytoma
Diet-mediated causes: • Alcohol • Caffeine • Licorice	Catecholamine-secreting tumors: • Pheochromocytoma • Neuroblastoma • Paraganglioma
Miscellaneous disorders: • Hypercalcemia • Lead poisoning • Orthopedic procedures (leg traction)	Low-renin hypertension • Gordon's syndrome • Apparent mineralocorticoid excess • Glucocorticoid remediable aldosteronism • Liddle syndrome
	Miscellaneous disorders: • Sickle cell anemia • Williams syndrome

ADPKD, autosomal dominant polycystic kidney disease; ARPDK, autosomal recessive polycystic kidney disease; NSAIDs, non-steroidal anti-inflammatory drugs.

artery accounts for the majority of these cases, but bilateral disease or intrarenal branch artery involvement with fibromuscular dysplasia can also be seen. Renal artery stenosis may also be seen in several clinical disorders and syndromes, including neurofibromatosis,[49–53] Marfan syndrome,[54] Takayasu disease,[55] and Klippel–Trénaunay–Weber syndrome.[56]

Coarctation of aorta

Coarctation of the aorta represents another potentially curable vascular-mediated form of hypertension. Its reported incidence has ranged from as low as 2%[57] to as high as 33% in a series of infants.[58] Although coarctation most commonly involves the thoracic aorta just below the origin of the left subclavian (>90%), it may occur at any point along the aorta. When coarctation occurs just above the renal arteries, it may extend into bilateral renal artery stenosis or other abdominal arteries, a constellation known as mid-aortic syndrome.[47,59,60] Mid-aortic syndrome may be caused by fibromuscular dysplasia or as part of the vascular pathology seen in neurofibromatosis,[49] Takayasu disease,[55] or Williams syndrome.[61]

Endocrine disorders

While hyperthyroidism is the most common endocrine disorder known to cause hypertension, abnormalities related to aldosterone excess can also be associated with hypertension in children. Indirect activation of amiloride-sensitive epithelial sodium channels (ENaC) on the apical surface of the principal cells of the renal cortical collecting ducts by aldosterone leads to sodium retention, with subsequent volume expansion, hypokalemia, and metabolic alkalosis.[62] Due to associated volume expansion in hyperaldosterone states, plasma renin activity is low to normal. Isolated overproduction of aldosterone may be seen in primary adrenal hyperplasia or aldosterone-producing adenomas (Figure 30.4). Both conditions are rare in the pediatric population, and distinction between the two may be difficult, since most adenomas are small (<1 cm),[63] and focal or diffuse hyperplasia of the remainder of the adrenal gland is common in the presence of an adenoma.[64]

Elevated aldosterone levels are also seen in patients with glucocorticoid-remediable aldosteronism (GRA). Considered to be the most common monogenic form of hypertension, GRA is an autosomal dominant disorder in which DNA encoding for aldosterone synthase is coupled to the regulatory sequences conferring adrenocorticotropic hormone (ACTH) responsiveness.[65] Thus, ACTH becomes the main controlling agent of aldosterone production rather than angiontensin II or potassium. Consequently, patients with GRA have aldosterone-mediated hypertension that can be suppressed with glucocorticoids. Activation of mineralocorticoid receptors in the kidney through substances other than aldosterone produces a similar clinical picture. Overproduction of other mineralocorticoids, as seen in several rare forms of congenital adrenal hyperplasia (CAH), is associated with hypertension mediated through this mechanism. 21-hydroxylase deficiency, considered the most common type of CAH (~90%), is not associated with hypertension, but 11β-hydroxylase, 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, and cholesterol desmolase deficiencies can cause hypertension.[66–68]

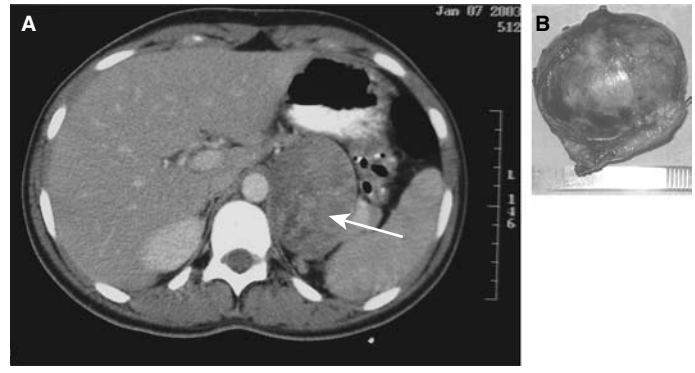

Figure 30.4 Adrenal adenoma in a 14-year-old girl with severe hypertension. Profound hypokalemia (potassium, 1.6 mmol/L) and metabolic alkalosis were documented in the emergency room. (A) CT scan showing the left adrenal tumor mass (arrow). (B) Tumor mass removed at surgery.

Elevated cortisol levels associated with Cushing's syndrome may also produce hypertension via a mineralocorticoid receptor effect. Although in-vivo aldosterone is 300 times more potent than cortisol in activating mineralocorticoid receptors, cortisol is able to produce an aldosterone effect if present in high enough concentrations.[69,70] This effect occurs as the threshold concentration for inactivating cortisol by 11β-hydroxysteroid dehydrogenase 2 is exceeded. This enzyme is found locally at mineralocorticoid receptor sites and converts cortisol to cortisone, conferring mineralocorticoid over glucocorticoid responsiveness to these receptors.[71] Genetic deficiencies in this enzyme have also been described in the autosomal recessive disease known as apparent mineralocorticoid excess (AME).[72]

Genetic disorders

Two other forms of monogenic hypertension are Liddle syndrome and Gordon's syndrome. Liddle syndrome is an autosomal dominant condition in which a mutation in the ENaC channel leads to persistent activation and sodium reabsorption.[73,74] This creates a clinical picture similar to hyperaldosteronism, but normal feedback mechanisms are no longer functional and renin and aldosterone levels are very low.[75] Gordon's syndrome (pseudohypoaldosteronism type II) is an autosomal dominant syndrome caused by mutations in the WNK1 and WNK4 kinase family, both of which are involved in regulating the activity of the thiazide-sensitive Na-Cl cotransporter in the distal nephron.[76,77] Hyperactivity of this receptor, as seen in Gordon's syndrome, leads to a clinical picture of salt reabsorption with subsequent low-renin hypertension, hyperkalemia, and metabolic acidosis.[75]

Neoplasma

Tumors may cause hypertension either by external compression of the renal artery or by the release of vasoactive substances

such as renin (Wilms' tumor) or catecholamines (pheochromocytomas). Hypertension caused by pheochromocytomas represents the most well-described syndrome in this category. Pheochromocytomas are usually benign tumors arising from chromaffin cell tissue in the adrenal medulla or other locations along the sympathetic chain, and rarely from atypical sites such as the bladder and heart.[78] The unregulated release of metanephrine or normetanephrine from these tumors leads to the classical symptoms of headaches, sweating, and palpitations with tachycardia.[79,80] Other common symptoms include anxiety, nausea and vomiting, and pallor. Whereas hypertension associated with these tumors is often considered to be intermittent, elevated BP is more often sustained in children, with periodic increases.[80] Urinary and plasma metanephrines are markedly elevated in patients with pheochromocytomas, although plasma metanephrines are more sensitive when obtained correctly.[81]

Localization of the tumor may prove more difficult. Usually an I^{131} or I^{123} meta-iodobenzylguanidine (I^{131} or I^{123} MIBG) scan is the initial scan used to identify tumors of neural crest origin, but the radionuclide scan may miss even large tumors.[82,83] Labeled somatostatin is an alternative way to identify catcholamine-secreting tumors missed by MIBG scans.[84] Magnetic resonance imaging (MRI) or computed tomography (CT) is needed to delineate tumor borders prior to surgery (Figure 30.5). Localization of a tumor with these modes of imaging should not be considered definitive, since finding multiple tumor foci is not uncommon, especially with syndromes involving pheochromocytomas such as neurofibromatosis,[85,86] von Hippel–Lindau disease,[87] and MEN (multiple endocrine neoplasia) syndromes.[88,89]

Whereas surgical removal of the tumor is the ultimate treatment for this type of hypertension, control of the hypertension initially with α blockade (such as with phenoxybenzamine), followed by β blockade if necessary, should be achieved until BP is controlled for at least 1 week prior to surgery.[90] β-blocking agents should not be used alone in these patients, since this results in unopposed stimulation of vascular α receptors and vasoconstriction, and can result in precipitation of a hypertensive crisis. Calcium channel blockers may also be used safely in this population if BP remains elevated despite α blockade.[91]

Essential hypertension

Although the exact cause and mechanism behind the development of essential hypertension have yet to be elucidated, many risk factors have been identified. Weight is one of the most strongly associated risk factors, with approximately 30% of obese adolescents identified as being hypertensive as well.[92] Diet and exercise, independent of weight, have also been suggested to be risk factors for hypertension. Specifically, a diet high in salt[93,94] and low in fresh fruits, vegetables, and calcium,[93] along with a sedentary lifestyle,[95] is associated with higher BP in adults. Evidence supporting the role of sodium in the development of hypertension in children is strong, but the role of other nutrients such as potassium and calcium is still unclear.[96,97]

Race and ethnicity also have some influence on the incidence of hypertension. A larger percentage of African-Americans in the United States have hypertension as compared with whites, Hispanics, and Native Americans.[98–100] Although sometimes difficult to separate from other implicated risk factors, high environmental stress levels in association with poverty or demanding environments have also been correlated with higher BP.[101] Finally, a number of genetic markers have been identified as possible contributors to the development of essential hypertension.

Neonatal hypertension

Hypertension in the neonatal population presents unique concerns than in older children and adolescents (Table 30.6). Umbilical artery catheter-associated thromboembolism, which may affect either the aorta and/or the renal arteries, accounts for the majority of cases of definable hypertension in this age group. Congenital lesions of both the vasculature and renal parenchyma – such as coarctation of the aorta, renal artery stenosis, polycystic kidney disease, and obstructive uropathy – also need to be considered as diagnostic possibilities in this age group. Hypertension has been reported in up to 43% of infants with bronchopulmonary dysplasia and many infants develop the condition after discharge from the NICU (neonatal intensive care unit), emphasizing the need for close monitoring and follow-up.[102,103] Likewise, up to 50% of infants requiring ECMO (extracorporeal membrane oxygenation) develop elevated

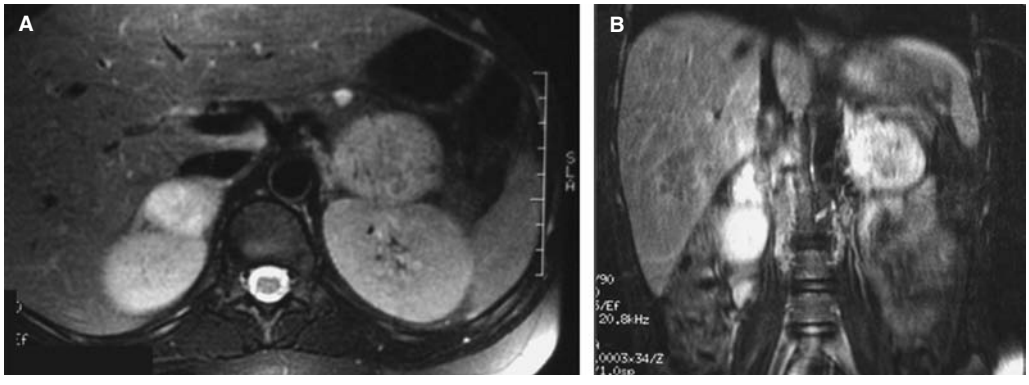

Figure 30.5 Pheochromocytoma in a 16-year-old male who presented with low-grade fever, recent weight loss, tachycardia, and hypertension. (A) Transverse MRI image showing the tumor mass in the left adrenal. (B) Coronal MRI image showing the tumor in the left adrenal gland above the kidney.

Table 30.6 Hypertension in the neonate

Congenital lesions and disorders listed in Table 30.5 should be considered, since these are common causes of hypertension in neonates as well, but additional considerations include:

- Umbilical catheter-associated embolic/thrombotic events
- Congenital nephrotic syndrome
- Idiopathic arterial calcification
- Congenital rubella syndrome
- Bronchopulmonary dysplasia
- Pneumothorax
- Pain
- Birth asphyxia
- Adrenal hemorrhage
- ECMO
- Closure of abdominal wall defects
- TPN
- Medications:
  - Vitamin D intoxication
  - Theophylline/caffeine
  - Phenylephrine
- Maternal drug use:
  - Cocaine
  - Heroin

ECMO, extracorporeal membrane oxygenation; TPN, total parenteral nutrition.

BP.[104,105] Finally, a number of iatrogenic causes have been implicated in neonatal hypertension, including medications (e.g. theophylline, caffine), maternal drug use (e.g. cocaine), and problems with prolonged parenteral nutrition (e.g. hypercalcemia and vitamins A and D intoxication).

Evaluation of a child with hypertension

Once a child has been identified as being hypertensive, a thorough evaluation aimed at identifying underlying causes, evaluating for target-organ damage, and assessing for other risk factors of cardiovascular disease should be undertaken. The urgency and rapidity with which the investigations should be undertaken is dependent on the severity of the child's hypertension. Patients suffering from hypertensive emergency and urgency, or those who are symptomatic, deserve immediate evaluation with concomitant therapeutic intervention. Milder elevations in BP can be evaluated at a more convenient pace.

Historical data

A detailed history should be obtained for all patients; it often provides clues for further diagnostic studies (Table 30.7). Many patients describe non-specific symptoms such as headaches, fatigue, and sleep disturbance, whereas complaints such as severe headaches, visual changes, and chest pain are more characteristic of severe hypertension. Hematuria and swelling suggest acute glomerulonephritis, whereas weight loss and sweating may indicate an endocrine abnormality or neuroendocrine tumor. Past medical history of UAC (umbilical artery catheter) placement or multiple infections during early childhood also

Table 30.7 Historical clues in the diagnosis of hypertension

Historical finding	Possible significance
Complaint/review of systems	
Headaches, dizziness, epistaxis, visual changes	Non-specific
Abdominal pain, dysuria, frequency, urgency, nocturia, enuresis	Underlying renal disease
Joint pains/swelling, edema, rashes	Autoimmune-mediated disease/glomerulonephritis
Weight loss, sweating, flushing, palpitations	Pheochromocytoma or hyperthyroidism
Muscle cramps, weakness, constipation	Hypokalemia associated with hyperaldosteronism
Delayed puberty	Congenital adrenal hyperplasia
Snoring	Sleep apnea
Prescription, over-the-counter, or illicit drug use	Drug-induced hypertension
Past medical history	
Umbilical artery catheterization	Renal artery thrombosis/renal embolus
Thyroid cancer, neurofibromatosis, von Hippel–Lindau disease	Pheochromocytoma
Family history	
Hypertension	Inherited forms of hypertension (AME, Gordon syndrome, Liddle syndrome, GRA), essential hypertension
Renal disease	Polycystic kidney disease, Alport syndrome
Tumors	Familial pheochromocytoma, MEN II
Early complications of hypertension and/or atherosclerosis	Predictive of hypertensive course

AME, apparent mineralocorticoid excess; GRA, glucocorticoid-remediable aldosteronism; MEN II, multiple endocrine neoplasia type II.

point to a renal-mediated cause. A thorough family, diet, sleep, and illicit drug use history may also provide clues toward the etiology of an individual's hypertension. In addition, a number of prescribed medicines have been shown to raise BP.

Physical examination

While a thorough physical examination is indicated for all patients, special care should be paid to findings suggestive of an underlying hypertensive disorder or end-organ damage (Table 30.8). On initial presentation, BP should be measured in all four extremities as a screening for coarctation, which should be suspected if upper extremity pressures are higher than lower extremity pressures. Weaker lower extremity pulses may also be appreciated in patients with coarctation. The remainder of the cardiac examination, including detection of carotid or abdominal bruits, may also provide clues for diagnosis. The head and neck examination may yield an enlarged thyroid or hypertensive retinopathy, whereas dermatologic examination may reveal striae, neurofibromas, or acanthosis nigricans. A neurologic examination may show signs of chronic or severe acute hypertension such as Bell's palsy or deficits such as hemiparesis.

Laboratory and imaging studies

Laboratory evaluation should include electrolytes to screen for monogenic forms of hypertension (generally associated with a hypokalemic metabolic alkalosis) and kidney function (blood urea nitrogen and creatinine) as well as assessing for anemia, which is associated with chronic kidney disease (CKD) and other chronic illnesses. Urinalysis to detect hematuria or proteinuria should be performed in all patients. The urine microalbumin/creatinine ratio should be obtained to assess for microalbuminuria – a finding common in adult patients with chronic hypertension but less common in children. Plasma renin activity (PRA) levels are useful to screen patients for renal, and renovascular diseases and for mineralocorticoid-related disorders. PRA is also elevated in patients with pheochromocytoma, whereas a low PRA is associated with hypertension caused by volume expansion and hyperaldosteronism. Specific laboratory studies, such as thyroid studies or urine catecholamines, should be conducted in patients with specific symptoms, or where particular diagnostic conditions are suspected. Finally, those patients with essential hypertension should be evaluated for hypercholesterolemia, hyperinsulinemia, and metabolic syndrome.

An echocardiogram is indicated in all patients with hypertension, and should evaluate for congenital anomalies such as coarctation as well as for left ventricular hypertrophy (LVH), a sensitive measure of end-organ damage. Presence of LVH should prompt more aggressive medical management. Serial testing may be a useful tool for monitoring therapeutic control and progression of hypertension.

A renal ultrasound is useful for identifying patients with parenchymal lesions, such as small scarred kidneys, polycystic

Table 30.8 Physical examination abnormalities in hypertensive patients

Clinical abnormality	Diagnostic implication
Vital signs	
Tachycardia	Hyperthyroidism, pheochromocytoma, neuroblastoma, primary hypertension
Drop in BP from upper to lower extremities	Coarctation
General	
Growth retardation	Chronic kidney disease
Obesity	Essential hypertension
Truncal obesity	Cushing disease, insulin resistance
HEENT	
Moon facies	Cushing disease
Elfin facies	Williams syndrome
Proptosis/goiter	Hyperthyroidism
Webbed neck	Turner syndrome
Adenotonsillar hypertrophy	Sleep disorders
Fundal changes	Chronic or severe hypertension
Cardiovascular	
Friction rub	SLE, collagen vascular disease, uremia
Apical heave	Left ventricular hypertrophy
Disparity in pulses	Coarctation
Lungs	
Crackles/rhales	Heart failure with chronic hypertension
Abdomen	
Masses	Obstructive nephropathy, Wilms' tumor, neuroblastoma, pheochromocytoma, polycystic kidney disease
Hepatomegaly	Heart failure
Bruit	Renal artery stenosis, abdominal coarctation
Genitalia	
Ambiguous, viralized	Congenital adrenal hyperplasia
Extremities	
Edema	Underlying kidney disease
Joint swelling	Autoimmune disease
Ricketsial changes	Chronic kidney disease
Dermatologic	
Neurofibromas	Neurofibromatosis
Tubers, ash-leaf spots, adenoma sebaceum	Tuberous sclerosis
Bronzed skin	Excessive ACTH
Acanthosis nigricans	Insulin resistance/metabolic syndrome
Striae, acne	Cushing disease
Rashes	Vasculitis/nephritis
Needle tracks	Drug-induced hypertension
Neurologic	
Encephalopathy	Severe hypertension
Cranial nerve palsy	Severe hypertension

BP, blood pressure; SLE, systemic lupus erythematosus; ACTH, adrenocorticotropic hormone.

kidney disease, or other structural anomalies. Compared with its use in adults, Doppler ultrasound is less sensitive in identifying subtle renal artery stenosis in children. Although magnetic resonance angiography has shown promise as a screening tool for renal artery stenosis (Figure 30.6), angiography remains the gold standard for identifying this lesion (Figure 30.7).[106–109] Other imaging tools, including a DMSA (digital subtraction angiography) scan, should be undertaken in patients with suspected renal scarring and suspicion of recurrent urinary tract infections (Table 30.9).

End-organ damage

With the rising prevalence of hypertension among children and adolescents, concerns regarding the morbidity and ultimate mortality associated with this condition are becoming increasingly relevant. For adults, hypertension is an independent risk factor for myocardial infarction, heart failure, stroke, and CKD.[6] Indeed, the World Health Organization reports that poor BP control is the dominant attributable risk for death in the world, and accounts for 62% of cerebrovascular disease and 49% of ischemic heart disease observed.[110] Hypertension is also the second leading cause of ESRD among adults requiring dialysis in the United States.[111]

The long-term effects of high BP on children and adolescents are difficult to evaluate due to the extended time interval necessary between diagnosis and a definable adverse event such as heart attack or stroke. However, measurable damage to the heart, blood vessels, retina, and kidneys have all been documented in young people with hypertension, sometimes at initial diagnosis. Also, it has been shown that children with high BP have an increased risk of continued hypertension as adults.[112–114]

LVH is the most commonly identified target-organ abnormality, occurring in 34–38% of children with hypertension.[115–117] LVH has been identified as an independent risk factor for the development of cardiovascular disease in adults,[118] and is well known to predict morbidity and mortality in this population.[119] The mechanisms whereby LVH increases the risk for cardiovascular disease are unknown, although abnormalities in diastolic function,[120] increased oxygen consumption that makes the cardiovascular system more susceptible to ischemia,[121] and induction of electrophysiologic abnormalities creating a risk for arrhythmias and sudden death[122] have all been suggested. Left atrial enlargement has also been associated with hypertension and cardiovascular disease in children, but its significance remains undetermined.[123]

Vascular damage has been identified in children with hypertension and is important because of its ability to affect a variety of different organs. Carotid artery intima-medial thickness (cIMT) measured via ultrasound has become an accepted marker of generalized atherosclerosis in adults and can be correlated with incident coronary artery disease, myocardial infarction, and stroke.[124–126] cIMT is increased in hypertensive children and is independently associated with BMI and left ventricular mass index.[116] Hypertensive retinopathy, another

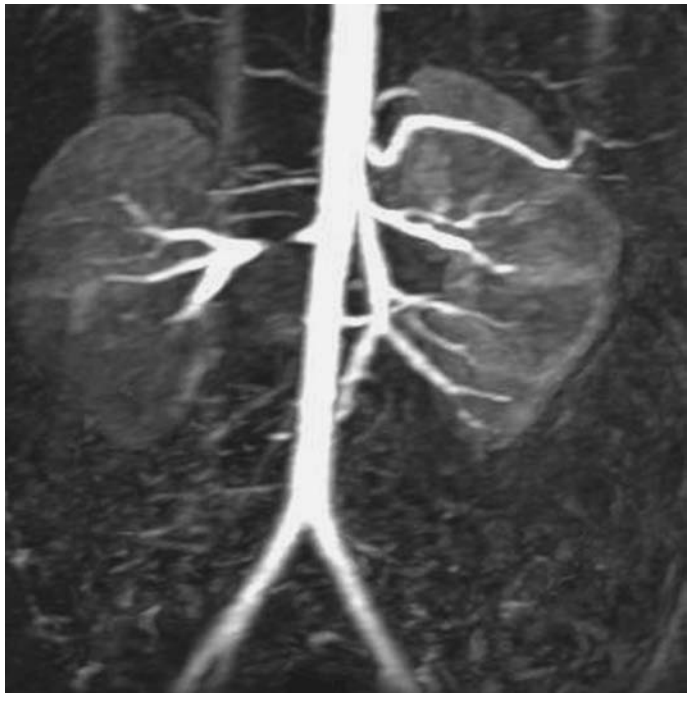

Figure 30.6 Renal artery stenosis in a patient visualized by a magnetic resonance arteriogram. The right renal main artery shows mid-segment stenosis.

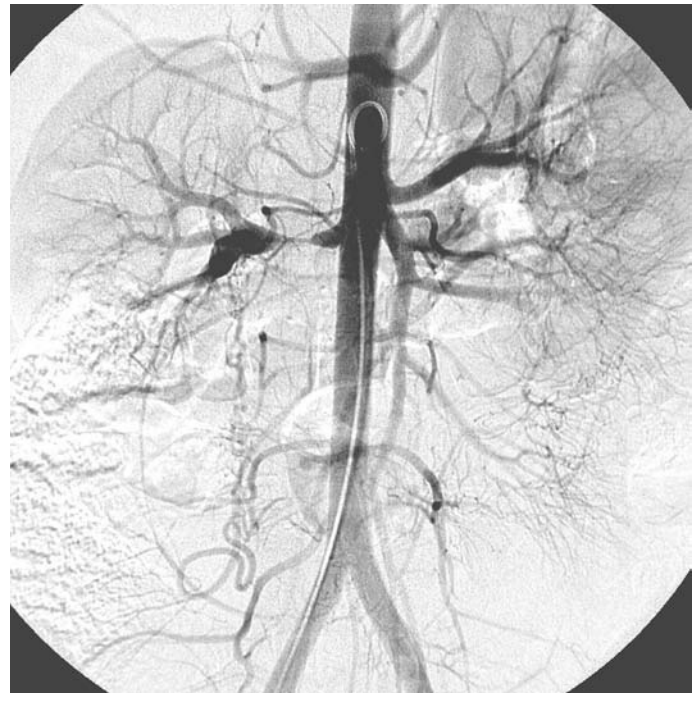

Figure 30.7 Renal arteriogram in the patient shown in Figure 30.6. Mid-segmental narrowing and poststenotic dilatation are clearly visible in the right renal artery.

Table 30.9 Clinical evaluation of confirmed hypertension

Study or procedure	Purpose	Target population
Evaluation for identifiable causes		
History, including sleep history, family history, risk factors, diet, and habits such as smoking and drinking alcohol; physical examination	History and physical examination help focus subsequent evaluation	All children with persistent BP ≥95th percentile
BUN, creatinine, electrolytes, urinalysis, and urine culture	R/O renal disease and chronic pyelonephritis	All children with persistent BP ≥95th percentile
CBC	R/O anemia, consistent with chronic renal disease	All children with persistent BP ≥95th percentile
Renal U/S	R/O renal scar, congenital anomaly, or disparate renal size	All children with persistent BP ≥95th percentile
Evaluation for comorbidity		
Fasting lipid panel, fasting glucose	Identify hyperlipidemia; identify metabolic abnormalities	Overweight patients with BP at 90–94th percentile; all patients with BP ≥95th percentile. Family history of hypertension or cardiovascular disease. Child with chronic renal disease
Drug screen	Identify substances that might cause hypertension	History suggestive of possible contribution by substances or drugs
Polysomnography	Identify sleep disorder in association with hypertension	History of loud, frequent snoring
Evaluation for target-organ damage		
Echocardiogram	Identify LVH and other indications of cardiac involvement	Patients with comorbid risk factors[a] and BP 90–94th percentile; all patients with BP ≥95th percentile
Retinal examination	Identify retinal vascular changes	Patients with comorbid risk factors[a] and BP 90–94th percentile; all patients with BP ≥95th percentile
Further evaluation as indicated		
Ambulatory BP monitoring	Identify white-coat hypertension, abnormal diurnal BP pattern, BP load	Patients in whom white-coat hypertension is suspected, and when other information on BP pattern is needed
Plasma renin determination	Identify low renin, suggesting mineralocorticoid-related disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension. Positive family history of severe hypertension
Renovascular imaging (captopril renal scan): • Isotopic scintigraphy (renal scan) • Magnetic resonance angiography • Duplex Doppler flow studies • 3-dimensional CT • Arteriography: DSA or classic	Identify renovascular disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine steroid levels	Identify steroid-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine catecholamines	Identify catecholamine-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension

BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; DSA, digital subtraction angiography; LVH, left ventricular hypertrophy; R/O, rule out; U/S, ultrasound.

[a]Comorbid risk factors also include diabetes mellitus and kidney disease.

Reproduced from Reference 7.

marker of vascular damage related to hypertension, has been well described in adults and is predictive of mortality in this population.[127] Although only a few studies of hypertensive retinopathy have been conducted in children and adolescents, retinal abnormalities may occur in up to 50% of infants with hypertension.[128]

Microalbuminuria (30–300 mg albumin/g creatinine in a first morning urine specimen) is indicative of early renal damage in adults, and is independently associated with adverse cardiovascular events.[129–131] However, this association has not been shown in children. This may be due to an increased prevalence of proteinuria in children or to a decreased sensitivity of the test at lower levels of injury. Children found to have microalbuminuria should be considered at risk for progression of hypertensive renal disease. Further research is needed to identify more sensitive markers for hypertensive nephropathy and effective intervention strategies to prevent the development of ESRD.

Clinical case

A 14-year-old African-American male presented to his pediatrician's office for his annual physical prior to joining the junior varsity football team. He denied any current concerns, although his mother reported that she thought he was overly tired and remembered that he complained of some dizziness during football practice toward the end of the season last year. He was born at term and had otherwise been relatively healthy for most of his life except for being slightly overweight. He was not taking any medications and denied any illicit drug use. He ate a 'typical' teenage diet and his favorite foods were pizza, nachos, and fried chicken. He ate few fresh fruits and vegetables, and consumed approximately 3 caffeinated beverages a day. Both his father and paternal grandfather had hypertension diagnosed in their 40s and 60s, respectively. His mother was recently diagnosed with diabetes mellitus.

Physical examination revealed a moderately overweight male in no distress. His height was at the 75th percentile for age and his BMI was 29. Vital signs were temperature 98.7° F, pulse 85/min, respirations 20/min, and BP 142/86 mmHg. He had mild acanthosis nigricans on the back of his neck but the remainder of his physical examination was normal. BP in four extremities was:

- right upper extremity, 140/76 mmHg
- left upper extremity, 132/68 mmHg
- right lower extremity, 134/66 mmHg
- left lower extremity, 130/64 mmHg.

Ninety-fifth percentile and 99th percentile of BP for height, age, and gender for this patient were 130/83 mmHg and 138/91 mmHg, respectively.

Comment

Being asymptomatic, the patient was instructed to return to the office for BP checks two more times over the next month. His average BP over all of these readings was 136/78 mmHg. He was diagnosed as having stage I hypertension. Serum electrolytes, renal function, complete blood count, urinalysis, urine microalbumin, insulin, and renal ultrasound were normal. His fasting triglycerides were elevated and an echocardiogram showed LVH. A dilated retinal examination by an ophthalmologist was normal. No underlying cause for his hypertension was discerned and the diagnosis of essential hypertension was made. The presence of LVH indicates an increased risk for cardiovascular disease in the future.

Concluding remarks

The prevalence of hypertension in children and adolescents is on the rise. Diagnosis requires attention to proper measurement techniques, consideration of underlying causes, and evaluation for end-organ damage and other cardiovascular risk factors. Early detection is essential to minimize the long-term health effects associated with hypertension.

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31 Management of hypertension in children and adolescents

Joseph T Flynn

Management of hypertension in adults is guided by evidence derived from the results of large-scale clinical trials such as ALLHAT that examine the effects of specific antihypertensive agents on cardiovascular morbidity and mortality.[1] In contrast, the management of hypertensive children and adolescents is still largely empiric. This is primarily due to the lack of long-term outcome data regarding non-pharmacologic and pharmacologic approaches to treatment of hypertension in children and adolescents.[2]

Despite paucity of data, the question of how to manage a child or teen with hypertension is faced by pediatric nephrologists and other practitioners every day. The purpose of this chapter is to update the reader on current approaches to the treatment of hypertensive children and adolescents, including the special cases of hypertensive neonates, hypertensive urgencies and emergencies, pheochromocytomas, and renal artery stenosis (RAS).

Management approach by stage of hypertension

Staging of hypertension is a concept well-known to those who care for hypertensive adults. This approach has been adopted for children and adolescents in the Fourth Report from the National High Blood Pressure Education Program (2004).[3] It is now recommended that elevated blood pressure (BP) in children and adolescents be staged in order to help guide the evaluation and management of pediatric patients with hypertension. Table 31.1 gives the staging criteria and outlines the recommended management approaches for each stage.

As can be seen in the table, intervention is recommended even for children or adolescents with blood pressures that fall into the 'prehypertension' range. Such children should be counseled regarding lifestyle changes and should be seen within 6 months for a repeat blood pressure measurement and assessment of how well they are adhering to the recommended lifestyle measures. At the other end of the scale, children or adolescents with stage 2 hypertension should have their blood pressure measurements repeated and a work-up initiated within a week. These patients are candidates for immediate institution of pharmacologic therapy. This staging system should be viewed as a framework within which to apply the specific measures discussed in subsequent sections of this chapter.

Non-pharmacologic management

Non-pharmacologic interventions have long been recommended as the starting point for treatment of hypertension in older children and adolescents. This is reflected in the recently issued Fourth Report from the National High Blood Pressure Education Program,[3] which emphasized the potential benefits of non-pharmacologic measures in not only reducing blood pressure in children with established hypertension but also in preventing the future development of more significant blood pressure elevation in children and adolescents with prehypertension.

Weight loss and exercise

Although the magnitude of change in BP may be modest, weight loss, aerobic exercise, and dietary modifications have all been shown to successfully reduce blood pressure in children and adolescents. Tracking studies provide the first line of evidence supporting the concept that weight reduction has the potential to control blood pressure in children. Blood pressure

Table 31.1 Classification of hypertension in children and adolescents, with measurement frequency and therapy recommendations

Stage	SBP or DBP percentile[a]	Frequency of BP measurement	Therapeutic lifestyle changes	Pharmacologic therapy
Normal	<90th	Recheck at next scheduled physical examination	Encourage healthy diet, sleep, and physical activity	–
Prehypertension	90th to <95th or if BP exceeds 120/80 mmHg, even if below 90th percentile up to <95th percentile[b]	Recheck in 6 months	Weight management counseling if overweight, introduce physical activity and diet management[d]	None unless compelling indications such as CKD, diabetes mellitus, heart failure, LVH
Stage 1 hypertension	95th percentile to the 99th percentile plus 5 mmHg	Recheck in 1–2 weeks or sooner if the patient is symptomatic; if persistently elevated on 2 additional occasions, evaluate or refer to source of care within 1 month	Weight management counseling if overweight; introduce physical activity and diet management[d]	Initiate therapy based on indications in Table 2 or if compelling indications as above
Stage 2 hypertension	>99th percentile plus 5 mmHg	Evaluate or refer to source of care within 1 week or immediately if the patient is symptomatic	Weight management counseling if overweight; introduce physical activity and diet management[d]	Initiate therapy[c]

BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
[a]For sex, age, and height measured on at least three separate occasions; if systolic and diastolic categories are different, categorize by the higher value.
[b]This occurs typically at 12 years old for SBP and at 16 years old for DBP.
[c]More than one drug may be required.
[d]Parents and children trying to modify the eating plan to the DASH eating plan (Appel et al[19]) could benefit from consultation with a registered or licensed nutritionist to get them started.
Reproduced from Reference 3.

clearly tracks from childhood through adolescence and into adulthood,[4] and the rise in BP in these studies is typically associated with an increase in body mass index (BMI).[5] Because of the strong correlation between weight and blood pressure, excessive weight gain is likely to be associated with elevated BP over time. Indeed, it has been recently demonstrated that the blood pressure of US children has increased over the past decade, and the major contributor to this increase is childhood obesity.[6] Therefore, maintenance of normal weight gain in childhood should prevent the development of hypertension in adulthood.

Several studies have demonstrated that weight loss in obese adolescents lowers BP.[7,8] Weight loss not only decreases blood pressure but it also improves other cardiovascular risk factors, such as dyslipidemia and insulin resistance.[9,10] A reduction in BMI of about 10% results in short-term reduction in blood pressure in the range of 8–12 mmHg. Unfortunately, weight loss is notoriously difficult and usually unsuccessful, especially in the primary care setting.[11] However, identifying a medical complication of obesity such as hypertension can perhaps provide the necessary motivation for patients and families to make the appropriate lifestyle changes.

With respect to exercise, sustained training over 3–6 months has been shown to result in a reduction of 6–12 mmHg for systolic blood pressure and 3–5 mmHg for diastolic blood pressure.[12] However, cessation of regular exercise is promptly followed by a rise in blood pressure to pre-exercise levels. Aerobic exercise activities such as running, walking, or cycling are usually preferred to static forms of exercise in the management of hypertension.[13] Many children may already be participating in one or more appropriate activities and may only need to increase the frequency and/or intensity of these activities (usually to at least 40–60 minutes/session, 4–5 times/week) to produce a reduction in their blood pressure.

It is important to emphasize that hypertension is not considered a contraindication to participation in competitive sports, so long as the child's blood pressure is 'controlled.'[14] Anecdotal experience suggests that treatment of hypertension in the competitive teen athlete may actually improve performance. However, it may be appropriate to restrict sports participation while the child's or adolescent's hypertension is being evaluated. Once a diagnosis has been made and treatment initiated, sports participation should be allowed. Indeed, the potential long-term benefits in terms of BP reduction

and weight control probably outweigh any possible risks of participation.

Diet

The role of dietary changes in the management of hypertension has received a great deal of attention, most of which has focused on sodium. Although it is controversial whether excessive sodium intake causes hypertension,[15] once hypertension has been established, 'salt sensitivity' becomes more common, and reduction in sodium intake is likely to be of benefit.[15–17] Other nutrients that have been examined in patients with hypertension include potassium and calcium, both of which have been shown to have antihypertensive effects.[17,18] Therefore, a diet that is low in sodium and enriched in potassium and calcium may be more effective in reducing blood pressure than a diet that restricts sodium only. An example of such a diet is the so-called DASH diet (Dietary Approaches to Stop Hypertension), which has been shown to have an antihypertensive effect in adults with hypertension, even in those receiving antihypertensive medication.[19] Although this diet has not been specifically studied in children or adolescents, the basic elements of the DASH eating plan are logical to apply to the treatment of hypertensive children, especially if accompanied by counseling from a pediatric dietitian. The DASH diet also incorporates measures designed to reduce dietary fat intake, an important strategy given the frequent presence of both hypertension and elevated lipids in children and adolescents and the imperative to begin prevention of adult cardiovascular disease at an early age as possible.[9,20,21]

Pharmacologic management

Historical perspective

The number of antihypertensive medications that have been systematically studied in children has increased markedly over the past 5 years due to incentives provided to the pharmaceutical industry under the auspices of the 1997 Food and Drug Administration Modernization Act (FDAMA) and the Best Pharmaceuticals for Children Act (BPCA) of 2002.[22,23] Whereas the 2000 Physicians Desk Reference contained FDA-approved pediatric dosing information for a minority of antihypertensive medications commonly used in children,[24] the 2004 Fourth Report[3] noted that FDA-approved dosing information is now available for at least a dozen such medications, including seven drugs for which pediatric trials have been conducted since 1999.

Thus, reliance on trial and error, or on adapting adult efficacy data, should no longer be necessary with antihypertensive therapy in children and adolescents. Since long-term, open-label extensions are now possible for clinical trials of antihypertensive medications in children,[23] evidence-based prescribing of these drugs in children should be achievable in years to come. Unfortunately, it is unlikely that long-term outcome studies of hypertension in children will ever be conducted, so the clinical benefit of prolonged pharmacologic therapy in hypertensive children may never be known.

Indications for pharmacotherapy

Experience in adults indicates that although blood pressure in some hypertensive patients may decline without treatment, in most it will likely persist and even progress over time.[25] This implies that once hypertensive patients are started medication, they are likely to remain on therapy for the rest of their life. This is readily accepted for adults, given the known long-term adverse consequences of untreated or undertreated hypertension.[26,27] However, since the long-term consequences of untreated hypertension in an asymptomatic, otherwise healthy, child or adolescent remain unknown,[2] the decision to prescribe antihypertensive medications in a child or adolescent should not be made lightly. Furthermore, even the open-label extensions to pediatric clinical trials of antihypertensive medications are insufficient to fully elucidate their long-term effects on the growth and development of children. Therefore, a clear indication for initiating pharmacotherapy should be established prior to commencing such treatment in children and adolescents.

Indications for use of antihypertensive medications in children and adolescents are listed in Table 31.2. Other indications for use of antihypertensive medications based upon the premise of reducing future risk of developing cardiovascular or end-stage renal disease have also been proposed, For example, the presence of multiple cardiovascular risk factors (elevated blood pressure, hyperlipidemia, tobacco use, etc.) increases cardiovascular risk in an exponential rather than additive fashion.[21,28] Thus, antihypertensive therapy might be instituted if the hypertensive child or adolescent is known to have hyperlipidemia. Similarly, elevated nocturnal blood pressure and/or blunted nocturnal dipping on ambulatory BP monitoring increases the likelihood of developing hypertensive target-organ damage and other adverse cardiovascular outcomes,[29,30] so nocturnal hypertension might also be a reasonable indication for pharmacotherapy.

Choice of antihypertensive agent

Recommendations for choice of antihypertensive medications in adults are based on ALLHAT and similar large-scale studies of hypertension treatment.[1,27] Many of these studies have compared the effects of different classes of antihypertensive agents

Table 31.2 Indications for antihypertensive drug therapy in children

Stage 2 hypertension
Symptomatic hypertension
Secondary hypertension
Hypertensive target-organ damage
Diabetes (types 1 and 2)
Persistent hypertension despite non-pharmacologic measures

on cardiovascular morbidity and mortality. Fortunately, traditional 'hard' cardiovascular end-points such as myocardial infarction are exceedingly rare in the pediatric age group, making it unlikely that comparable studies will ever be conducted in children. Given this, the choice of initial antihypertensive agent for use in children still remains up to the preference of the individual practitioner.

Diuretics and β-adrenergic blockers, which were recommended as initial therapy in the First and Second Task Force Reports,[31,32] have a long track record of safety and efficacy in hypertensive children and are still appropriate for pediatric use, although they are now mostly used as second-line agents. Similarly, newer classes of agents, including angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), and angiotensin receptor blockers (ARBs), have now been shown to be safe and well tolerated in hypertensive children in recent industry-sponsored trials, and may be prescribed if indicated.[33–37] As noted in the 1996 Working Group Report, these newer agents, particularly CCBs and ACEIs, have become the most widely utilized initial agents in the pediatric age group.[38]

Consideration should be given to using specific classes of antihypertensive medications in certain hypertensive children and adolescents with specific underlying or concurrent medical conditions. The best example of this would be the use of ACEIs or ARBs in children with diabetes or proteinuric renal diseases.[39] This parallels the approach outlined in the JNC-7 report, which recommends that specific classes of antihypertensive agents be used in adults if compelling indications are present,[27] and is consistent with prior expert recommendations that the therapy of childhood hypertension should be tailored to the specific clinical status of the individual patient.[40]

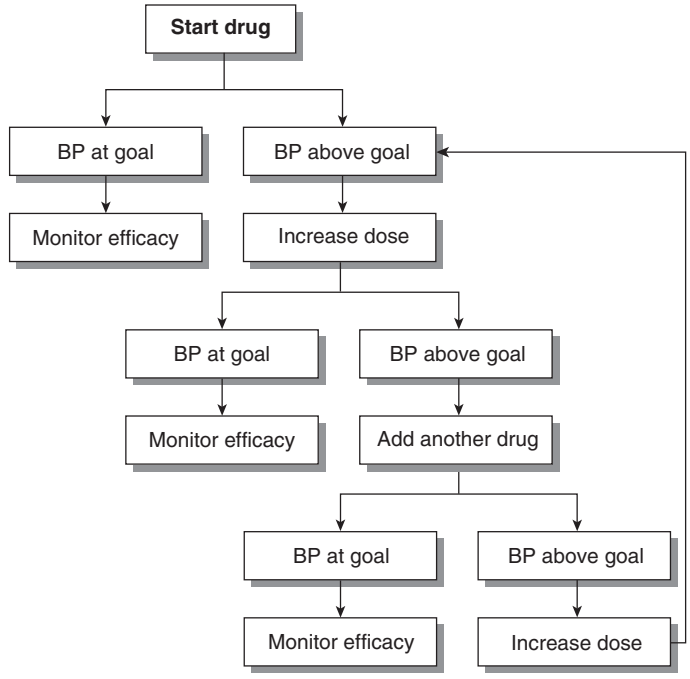

Figure 31.1 Stepped-care approach to prescribing antihypertensive drugs in children. BP, blood pressure.

Approach to prescribing

As illustrated in Figure 31.1, antihypertensive drugs in children and adolescents are generally prescribed in a stepped-care manner. The patient is started on the lowest recommended dose of the initial agent and the dose is increased until the highest recommended dose is reached, or until the child experiences adverse effects from the medication. At this point a second drug from a different class should be added, until the desired goal BP is reached. Since many antihypertensive drugs now have specific FDA-approved pediatric labeling, the generalist should restrict their choices to those agents. Recommended doses for selected antihypertensive agents for use in hypertensive children and adolescents are given in Table 31.3.

Our usual approach is to begin with a long-acting calcium channel blocker or ACEI, then add either a diuretic or β blocker as the second agent. Many children and adolescents with 'uncomplicated' primary hypertension may require two or more drugs to achieve target BP. Children with secondary hypertension, particularly those with renal disease, almost always require multidrug regimens to achieve adequate BP control. Combination antihypertensive preparations are now available and offer advantages that may improve adherence to treatment.[40] Thus far, only one such preparation has been studied in children,[41] so it is difficult to recommend their widespread use at this time. However, they may be very useful in certain children, particularly those who require an ACEI or ARB plus a diuretic; many preparations offering this combination are available.[40]

Goals of therapy

For children with uncomplicated primary hypertension and no hypertensive target-organ damage, the target BP should be < 95th percentile for age, gender, and height, whereas for children with secondary hypertension, diabetes, or hypertensive target-organ damage, target BP should be < 90th percentile for age, gender, and height.[3] These goals are akin to current recommendations for therapy of hypertension in adults[27] and also parallel the prescribing practices of many pediatric nephrologists.[39]

Long-term issues in hypertension treatment

Treatment of childhood hypertension does not end with the decision to prescribe antihypertensive medication. Ongoing monitoring of BP, surveillance for medication side effects, periodic monitoring of electrolytes (in patients treated with ACEIs, ARBs or diuretics), counseling regarding other cardiovascular

Table 31.3 Recommended doses for selected antihypertensive agents for use in hypertensive children and adolescents

Class	Drug	Starting dose	Interval	Maximum dose[a]	Adverse effects/other comments
Angiotensin-converting enzyme inhibitors (ACEIs)	Benazepril[b]	0.2 mg/kg/day up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg qd	1. Monitor serum chemistries shortly after initiating therapy and periodically thereafter 2. Contraindicated in patients with bilateral RAS or RAS in single kidney, and in pregnancy 3. May cause cough and angioedema 4. Many ACEIs are available in combination preparations containing a diuretic
	Captopril[b]	0.3–0.5 mg/kg/dose	bid–tid	6 mg/kg/day up to 450 mg/day	
	Enalapril[b]	0.08 mg/kg/day	qd	0.6 mg/kg/day up to 40 mg/day	
	Fosinopril	0.1 mg/kg/day up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg/day	
	Lisinopril[b]	0.07 mg/kg/day up to 5 mg/day	qd	0.6 mg/kg/day up to 40 mg/day	
	Quinapril	5–10 mg/day	qd	80 mg/day	
Angiotensin receptor blockers (ARBs)	Candesartan	4 mg/day	qd	32 mg qd	1. Monitor serum chemistries shortly after initiating therapy and periodically thereafter 2. Contraindicated in patients with bilateral RAS or RAS in single kidney, and in pregnancy 3. Many ARBs are available in combination preparations containing a diuretic
	Irbesartan	75–150 mg/day	qd	300 mg/day	
	Losartan[b]	0.75 mg/kg/day up to 50 mg/day	qd	1.4 mg/kg/day up to 100 mg/day	
α and β antagonists	Labetalol[b]	2–3 mg/kg/day	bid	10–12 mg/kg/day up to 1.2 g/day	1. Contraindicated in asthma, heart failure (labetalol only), and diabetes 2. Heart rate is dose-limiting 3. May impair athletic performance 4. Carvedilol beneficial in heart failure
	Carvedilol	6.25–12.5 mg bid	bid	25 mg bid	
β antagonists	Atenolol[b]	0.5–1 mg/kg/day	qd–bid	2 mg/kg/day up to 100 mg/day	1. Propranolol contraindicated in asthma, heart failure 2. Heart rate is dose-limiting 3. May impair athletic performance 4. Should not be used in insulin-dependent diabetics 5. Sustained-release formulations of propranolol and metoprolol are available that are dosed once daily
	Bisoprolol/HCTZ	2.5/6.25 mg/day	qd	10/6.25 mg qd	
	Metoprolol	1–2 mg/kg/day	bid	6 mg/kg/day up to 200 mg/day	
	Propranolol	1 mg/kg/day	bid–tid	16 mg/kg/day up to 640 mg/day	

(Continued)

Table 31.3 (Continued)

Class	Drug	Starting dose	Interval	Maximum dose[a]	Adverse effects/other comments
Calcium channel blockers	Amlodipine[b] Felodipine Isradipine[b] Extended-release nifedipine	0.06 mg/kg/day 2.5 mg/day 0.05–0.15 mg/kg/dose 0.25–0.5 mg/kg/day	qd qd tid–qid qd–bid	0.3 mg/kg/day up to 10 mg/day 10 mg/day 0.8 mg/kg/day up to 20 mg/day 3 mg/kg/day up to 120 mg/day	1. Felodipine and extended-release nifedipine tablets must be swallowed whole 2. May cause mild tachycardia, flushing and headache 3. Gingival hyperplasia may occur with prolonged use, especially in combination with calcineurin inhibitors
Central α agonists	Clonidine[b] Methyldopa[b]	5–10 μg/kg/day 5 mg/kg/day	bid–tid bid–qid	25 μg/kg/day up to 0.9 mg/day 40 mg/kg/day up to 3 g/day	1. May cause dry mouth and sedation 2. Clonidine also available in a transdermal preparation 3. Sudden withdrawal of clonidine may cause severe rebound hypertension
Diuretics	Amiloride Chlorothiazide Chlorthalidone Furosemide HCTZ Spironolactone[b] Triamterene	5–10 mg/day 10 mg/kg/day 0.3 mg/kg/day 0.5–2.0 mg/kg/dose 0.5–1 mg/kg/day 1 mg/kg/day 1–2 mg/kg/day	qd bid qd qd–bid qd qd–bid bid	20 mg/day 20 mg/kg/day up to 1.0 g/day 2 mg/kg/day up to 50 mg/day 6 mg/kg/day 3 mg/kg/day up to 50 mg/day 3.3 mg/kg/day up to 100 mg/day 3–4 mg/kg/day up to 300 mg/day	1. Electrolytes should be monitored shortly after initiating therapy and periodically thereafter 2. All diuretics are best used as add-on therapy in combination with other classes of antihypertensives 3. Chlorothiazide and furosemide are commercially available as suspensions
Peripheral α antagonists	Doxazosin Prazosin Terazosin	1 mg/day 0.05–0.1 mg/kg/day 1 mg/day	qd tid qd	4 mg/day 0.5 mg/kg/day 20 mg/day	All may cause first-dose hypotension
Vasodilators	Hydralazine Minoxidil	0.25 mg/kg/dose 0.1—0.2 mg/kg/day	tid–qid bid–tid	7.5 mg/kg/day up to 200 mg/day 1 mg/kg/day up to 50 mg/day	1. Tachycardia and fluid retention are common side effects 2. Hydralazine can cause a lupus-like syndrome in slow acetylators 3. Prolonged use of minoxidil can cause hypertrichosis

bid, twice daily; HCTZ, hydrochlorothiazide; qd, once daily; qid, four times daily; RAS, renal artery stenosis; tid, three times daily.

[a]The maximum recommended adult dose should never be exceeded.

[bc]Information on preparation of a stable extemporaneous suspension is available for these agents.

risk factors, and continued emphasis on therapeutic lifestyle changes also need to be incorporated into the management plan. Home BP measurement can be helpful in ensuring that BP control has been achieved. In some patients, repeat ambulatory BP monitoring may be necessary if office BP measurements appear to indicate 'resistant hypertension'. Hypertensive target organ damage such as left ventricular hypertrophy, if present, should be reassessed periodically.[3]

It may also be appropriate to consider withdrawal of drug therapy in selected children and adolescents. This involves an attempt at gradual reduction in medication following an extended course of good BP control, with the eventual goal of discontinuing drug therapy. Although no comparable studies have yet been performed in children, experience in adults suggests that a substantial percentage of patients may remain normotensive after withdrawal of active treatment.[25] Children and adolescents with obesity and uncomplicated primary hypertension who successfully lose weight and maintain their weight loss are the best candidates for this 'step-down' approach. These children should receive continued BP monitoring after drug therapy is withdrawn, and should continue non-pharmacologic treatment.

Special clinical issues

Hypertension in infancy

These are fewer data available on the efficacy and safety of antihypertensive agents in infants than there are for older children. Only recently have industry-sponsored clinical trials been extended to children less than 6 years of age.[23] Trials in infants less than 1 year of age may never be conducted. Therefore, use of antihypertensive medications in infants is largely based upon expert opinion and data derived from experience in older patients.

Indications for starting antihypertensive drugs in infants are driven by clinical circumstances. In general, critically ill premature infants with persistent BP elevation above published normative values[42] should be promptly treated. More stable neonates should probably be treated if the majority of BP readings over a 24–36-hour period are elevated. For older infants, particularly those that have been discharged from the nursery and are being followed as outpatients, BP should be confirmed to be elevated over several weeks before drug treatment is initiated.

As in older patients, therapy of hypertensive infants should be tailored to the severity of the hypertension and the infant's overall clinical status.[43] For example, critically ill infants with severe hypertension should be treated with an intravenous agent administered by continuous infusion, as this will allow the greatest control over the magnitude and rapidity of the BP reduction. On the other hand, relatively well infants with mild hypertension may be treated with oral antihypertensive agents. Recommended doses for both intravenous and oral antihypertensive drugs in infants can be found in Table 31.4.

Most classes of antihypertensive drugs used in older children have been applied to the treatment of hypertensive infants, and probably most can be safely used when treatment is indicated. The one exception to this, at least on theoretical grounds, is probably ACEIs. The renin–angiotensin system is crucial to normal renal development, both prenatally and postnatally. Experimental data indicate that exposure of the immature kidney to ACE inhibition may impair the completion of normal development and even cause histopathologic lesions.[44,45] Thus, it may be appropriate to avoid ACEIs in infants until they have reached a corrected postnatal age of 3–6 months.

Hypertensive emergencies

The pathophysiology, management, and outcome of severe hypertension in children and adolescents have been reviewed in detail elsewhere.[40,46] Perhaps the most important aspect to highlight here is that hypertensive encephalopathy occurs frequently in children and adolescents with severe hypertension, particularly in younger children. Given this, it is clear that BP reduction in such patients should be performed in a slow, controlled fashion to prevent ischemic strokes and other complications arising through loss of normal autoregulatory processes.[46–49]

Although evidence-based recommendations are lacking, the usual goal in treatment of a hypertensive emergency is to reduce the BP by no more than 25% over the first 8 hours, with a gradual return to normal/goal BP over 24–48 hours.[46,49] Given the need for controlled BP reduction, treatment of hypertensive emergencies in children and adolescents should be initiated with a continuous infusion of an intravenous antihypertensive, with nicardipine and labetalol finding the greatest popularity in many centers.[49,50] The dopamine receptor agonist fenoldopam has also been reported effective,[51] although it may not be as potent as nicardipine or other agents.[52]

For less-severe degrees of BP elevation, or if the child's symptoms permit, oral antihypertensive agents can be used. The choice of oral antihypertensives for use in management of severe hypertension remains a topic of debate among pediatric nephrologists,[53] with short-acting nifedipine advocated as safe by some authors,[54,55] and as dangerous by others.[56] Clearly, more data in this unique patient population will be needed to definitively answer this question.[57] A list of recommended doses for drugs used to treat severe hypertension in children and adolescents can be found in Table 31.5.

Pheochromocytoma

Although rare as a cause of hypertension in childhood,[58] pheochromocytomas present a unique set of management challenges. Many children with pheochromocytomas initially present with severe, symptomatic hypertension of unknown etiology.[59] Such children require careful immediate stabilization and gradual BP reduction, as described in the preceding section, until such time as the necessary studies can be obtained to

Table 31.4 Recommended doses for selected antihypertensive agents for treatment of hypertensive infants

Class	Drug	Route	Dose	Interval
Angiotensin-converting enzyme inhibitor	Captopril	Oral	<3 months: 0.01–0.5 mg/kg/dose Max 2 mg/kg/day >3 months: 0.15–0.3 mg/kg/dose Max 6 mg/kg/day	tid
	Enalapril	Oral	0.08–0.6 mg/kg/day	qd-bid
α and β antagonist	Labetalol	Oral	0.5–1.0 mg/kg/dose Max 10 mg/kg/day	bid–tid
		IV	0.20–1.0 mg/kg/dose 0.25–3.0 mg/kg/h	q 4–6 hours Infusion
β antagonist	Esmolol	IV	100–300 μg/kg/min	Infusion
	Propranolol	Oral	0.5–1.0 mg/kg/dose Max 8–10 mg/kg/day	tid
Calcium channel blocker	Amlodipine	Oral	0.05–0.3 mg/kg/dose Max 0.3 mg/kg/day	qd–bid
	Isradipine	Oral	0.05–0.15 mg/kg/dose Max 0.8 mg/kg/day	qid
	Nicardipine	IV	1-4 μg/kg/min	Infusion
Diuretic	Chlorothiazide	Oral	5–15 mg/kg/dose	bid
	Hydrochlorothiazide	Oral	1–3 mg/kg/dose	qd
	Spironolactone	Oral	0.5–1.5 mg/kg/dose	bid
Vasodilator	Hydralazine	Oral	0.25–1.0 mg/kg/dose Max 7.5 mg/kg/day	tid qid
		IV	0.15–0.6 mg/kg/dose	q 4 hours
	Minoxidil	Oral	0.1–0.2 mg/kg/dose	bid–tid
	Sodium nitroprusside	IV	0.5–10 μg/kg/min	Infusion

bid, twice daily; IV, intravenous; q, every; qd, once daily; qid, four times daily; tid, three times daily.
For comments on adverse effects, see Table 31.3.

establish the diagnosis. Although theoretically the α- and β-blocking agent labetalol may seem uniquely well suited for treatment of hypertension caused by a pheochromocytoma, in practice a continuous infusion of any of the intravenous antihypertensives listed in Table 31.5 could be utilized for initial BP management. Phentolamine has also been advocated in such patients, although pediatric experience with this agent is extremely limited.[60]

Once the diagnosis of pheochromocytoma has been made, the child's BP should be stabilized until the tumor can be surgically removed. Phenoxybenzamine, a potent α-adrenergic blocker, is usually recommended as the primary agent for this phase of management.[60,61] Other drugs have been reported to be successful as well.[59,60] The phenoxybenzamine dose is increased gradually (every 48 hours) until the desired BP control and α-adrenergic blockade is achieved. β-adrenergic blockade is frequently advocated as adjunctive therapy to counter tachycardia in patients treated with phenoxybenzamine.

Definitive treatment of pheochromocytoma requires either open or laparoscopic removal of the tumor. In addition to strict blood pressure control as discussed above, preoperative management also includes volume replacement and monitoring for arrhythmias produced by surges of catecholamine release from the tumor.[58–60] Intraoperatively, BP surges and arrhythmias may occur due to manipulation of the tumor. These complications can be treated with use of rapidly acting intravenous antihypertensive agents and β-adrenergic blockade. Volume resuscitation may be required immediately following removal of the tumor.[59] Although successful tumor removal should result in cure of the child's hypertension, periodic monitoring of plasma catecholamines and metanephrines should be performed to detect potential tumor recurrence.

Renovascular hypertension

Although the term 'renovascular hypertension' can be used to describe hypertension caused by a variety of conditions, it often implies hypertension secondary to renal artery stenosis. Children with RAS may have acute presentations with severe, symptomatic hypertension, or they may be asymptomatic.[62]

Table 31.5 Recommended doses for antihypertensive agents used for hypertensive emergencies and urgencies in children and adolescents

Drug	Class	Dose	Route	Comments
Clonidine	Central α agonist	0.05–0.1 mg/dose, may be repeated up to 0.8 mg total dose	Oral	Side effects include dry mouth and sedation
Enalaprilat	ACEI	0.05–0.10 mg/kg/dose up to 1.25 mg/dose	IV bolus	May cause prolonged hypotension and acute renal failure
Esmolol	β blocker	100–500 μg/kg/min	IV infusion	Very short-acting. May cause profound bradycardia
Fenoldopam	Dopamine receptor agonist	0.2–0.8 μg/kg/min	IV infusion	Produced modest reductions in BP in a pediatric clinical trial in patients up to 12 years
Hydralazine	Vasodilator	0.2–0.6 mg/kg/dose	IV, IM	Should be given every 4 hours when given IV bolus
Isradipine	Calcium channel blocker	0.05–0.1 mg/kg/dose	Oral	Stable suspension can be compounded
Labetalol	α and β blocker	bolus: 0.20–1.0 mg/kg/dose up to 40 mg/dose infusion: 0.25–3.0 mg/kg/h	IV bolus or infusion	Asthma and overt heart failure are relative contraindications
Minoxidil	Vasodilator	0.1–0.2 mg/kg/dose	Oral	Most potent oral vasodilator; long-acting
Nicardipine	Calcium channel blocker	1–3 μg/kg/min	IV infusion	May cause reflex tachycardia
Sodium nitroprusside	Vasodilator	0.5–10 μg/kg/min	IV infusion	Monitor cyanide levels with prolonged (>72 h) use or in renal failure; or co-administer with sodium thiosulfate

ACEI, angiotensin-converting enzyme inhibitor; IM, intramuscular; IV, intravenous.

As in other forms of secondary hypertension, initial BP control can be achieved with any of a variety of available antihypertensive agents, particularly vasodilators. Addition of a diuretic can greatly improve BP control, since a component of fluid volume overload is usually present in these patients with RAS, especially with unilateral disease.

The use of ACE inhibitors in patients with RAS is controversial. They are clearly contraindicated in bilateral RAS, or in RAS with a single kidney (including RAS in transplanted kidneys) due to the risk of inducing acute renal failure.[63] However, they may be very effective in cases when RAS is unilateral and surgery or angioplasty is unable to be performed, or when intrarenal stenoses are present that are not amenable to surgery or angioplasty.[64] In such cases, serial ultrasonography to follow renal growth and/or serial nuclear scans to follow renal perfusion may be helpful in determining whether to continue ACEIs.

As hypertension caused by RAS is potentially curable, the chief issue in managing children with renovascular hypertension is whether and/or when they should undergo angioplasty or surgical revascularization.[64] Although percutaneous transluminal angioplasty (PCTA) offers the advantage of being less invasive than surgical revascularization (Figure 31.2), results in children with renovascular hypertension may not be as good as in adults, primarily because RAS in children is typically caused by fibromuscular dysplasia, and may be associated with either multiple stenoses or intrarenal branch vessel stenoses.

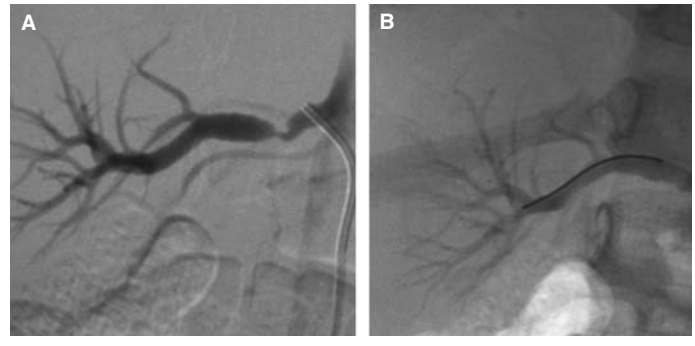

Figure 31.2 (A) Renal arteriogram showing renal arterial stenosis in the mid-arterial position. (B) Angiogram showing normal blood flow after balloon angioplasty of the renal artery.

This contrasts with RAS in adults, which is typically related to build-up of atherosclerotic plaque at the origin of the renal arteries. In a recent large series, 48 PCTA procedures were performed in 33 children, some of whom required multiple procedures because of restenosis or bilateral disease. Most children had improvement of BP following PCTA, although only 11 were normotensive off all medications.[62]

Surgical revascularization, while admittedly more invasive than PCTA, seems to offer a greater likelihood of complete cure of the child's hypertension. At the University of Michigan, for

example, 79% of children who underwent various revascularization procedures were considered cured.[65] Surgery is preferred to PCTA in children with multiple stenoses,[66] and can also be successful when PCTA has failed.[62]

Finally, although PCTA and surgery for RAS have been performed in very young children[65,67] when renovascular hypertension is diagnosed in an infant or toddler, it may be prudent to manage the child medically until they have grown sufficiently so that a definitive procedure can be safely performed. In such children, careful follow-up with serial renal ultrasonography to assess renal growth and serial echocardiograms to monitor for the development of left ventricular hypertrophy can be crucial in determining when surgery or PCTA should be undertaken.

Concluding remarks

The treatment of hypertensive children and adolescents can be both challenging and rewarding to the clinician. Non-pharmacologic and pharmacologic approaches should be utilized as appropriate, although non-pharmacologic measures should always be incorporated into each patient's regimen. Fortunately, the amount of information regarding antihypertensive drug efficacy and safety in children is much greater now than in the recent past. This should improve the management of hypertensive children and adolescents by enabling physicians to prescribe with greater confidence that drug theraphy will be beneficial, not harmful, to them.

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Part VII

Developmental and urologic disorders

32 Syndromic renal disorders and malformations

Dina J Zand and Kenneth N Rosenbaum

Isolated malformations and genetic disorders contribute significantly to pediatric morbidity and mortality.[1,2] In a child with a urogenital malformation, diagnosed either prenatally or after birth, the challenge is to determine whether the malformation is isolated, related to an exposure within the prenatal environment, or has an underlying genetic basis. Identification of additional malformations, prognosis, and determination of familial risk are also necessary in such patients. Recent advances in technology have been crucial in elucidation of the molecular origin of many syndromes.

Definitions of genetic disorders

The discipline of dysmorphology in clinical genetics focuses on patterns of abnormal development. Recent advances in the Human Genome Project have yielded explanations as to how a specific DNA mutation or chromosomal deletion may correlate with the descriptions of a clinical dysmorphologist. The role of a clinical geneticist is to organize any abnormal clinical, radiologic, or laboratory findings into one of four categories (Table 32.1).[3,4]

Genetic disorders may be caused by single gene defects, chromosomal abnormalities, or other modes of inheritance, such as methylation abnormalities or multifactorial inheritance. Table 32.2 summarizes common cytogenetic and molecular terminology used in reference to genetic disorders.

Single gene defects

Genes are the smallest functional unit in the chromosome; they encode for proteins involved in normal cell processes and embryonic developmental programming.[5] An estimated 20 000 to 25 000 genes reside in the human genome. Single gene defects are caused by mutations, either within the coding sequence of a gene, or in the DNA sequences responsible for expression of the gene. A mutation in a gene may affect the quality and subsequent functionality of the protein that the gene controls. Phenotypic or clinical expression may require involvement of a single copy or both copies of the gene. Table 32.3 lists terms that describe the expression pattern or effect on phenotype of gene mutations, particularly within a family.

Chromosomal disorders

Chromosomal disorders occur when there is either excess, or deficit of chromosomal material in the cells. This results in an imbalance in comparison to the normal cellular milieu.

Methylation defects

Methylation is a normal cellular process, and involves the placement of a methyl group on DNA base pairs to indicate transcriptional inactivity. When the cell lacks appropriate placement of the methyl group, disruption of normal cellular processes results. Beckwith–Wiedemann syndrome is an example of a methylation defect. Methylation abnormalities often have an association with the parent of origin (POR) for a chromosome. Here, if one parent provides two of the same autosomes – chromosome 11, for example – the *imprinting* (or methylation) of the chromosome will be abnormal and results in the phenotype.

Multifactorial inheritance

Multifactorial inheritance is defined as a mutation within a gene, which, in combination with other factors, such as environmental or genetic modifiers, affects the phenotype and produces a malformation.

Single gene inheritance

Autosomal dominant

Autosomal dominant inheritance is characterized by a mutation in a single gene affecting only one of the two chromosomes

Table 32.1 Terms used in describing genetic and developmental disorders

Term	Definition	Example
Malformation	A morphologic defect of an organ, part of an organ, or larger region of the body resulting from an abnormal developmental process programmed on a cellular and molecular level	Heterotaxy
Major	Malformations that require medical or surgical intervention, or of cosmetic significance	Congenital heart defect
Minor	Malformations where there is tissue or an organ with unusual morphology, but otherwise has features of no significance	Cupped ears
Disruption	A morphologic defect due to the extrinsic breakdown of tissue in an otherwise normal developmental process	Amniotic band syndrome
Deformation	An abnormal form, shape, or position of part of the body due to mechanical forces	Equinovarus due to oligohydramnios
Dysplasia	Abnormal organization of cells into tissues, resulting in a morphologic abnormality	Cutis aplasia
Syndrome	Multiple malformations that are related on a pathogenetic level	Down syndrome
Association	The non-random occurrence of more than one anomaly that may not be part of a syndromic diagnosis	Ear pits and renal malformations
Field defect	Describes a pattern of anomalies that was caused by the disturbance of a single developmental field, or functional embryologic unit	Poland anomaly – absence of the pectoralis muscle and associated hand abnormal development
Sequence	A pattern of multiple anomalies subsequently derived from a single known anomaly or mechanical factor	Sacral agenesis – often associated with maternal diabetes

Table 32.2 Diagnostic methodology used in identifying genetic disorders

Test	Description	Utilization
Karyotype	Photograph of the number of chromosomes in a cell, often after staining with a material that binds to specific DNA residues to elicit a characteristic pattern. Giemsa staining is the most commonly used	Identifies large areas of chromosome deletion, duplication, or rearrangement
p	Short arm of the chromosome	
q	Long arm of the chromosome	
deletion	Missing cytogenetic material, often noted as a minus sign on karyotype	
duplication	Additional cytogenetic material, often noted as a plus sign on karyotype	
FISH	Fluorescence in situ hybridization – fluorescently labeled DNA used as a probe to identify chromosomal microdeletions or duplications	Identifies microdeletions or duplications not seen on karyotype
PCR	Polymerase chain reaction – molecular amplification of specific DNA sequences	Can identify mutation or areas of DNA expansion
MS	Mass spectroscopy	Utilized to identify molecules based on size and/or charge. Used to evaluate amino acid, organic acid, and fatty oxidation disorders

where the involved gene is located. This single mutation is sufficient to result in an abnormal phenotype, and a person is said to be heterozygous for the trait (Figure 32.1). Many autosomal dominant traits are caused by spontaneous mutation, where the mutation originated in either the embryo of the affected individual or the gamete of one of the parents. A common example of spontaneous mutation is neurofibromatosis type I (NF-1). The term sporadic usually refers to the first affected member within a family. Microdeletion syndromes, which often occur in a sporadic manner, can be passed on in an autosomal dominant fashion.

Autosomal recessive

In autosomal recessive inheritance, an affected individual has received two mutated copies of the same gene, one from each parent (Figure 32.2). The affected proband is said to be homozygous for the trait. In this mode of inheritance, both parents are said to be obligate carriers of the mutated gene but do not demonstrate clinical or biochemical manifestations of the disease themselves.

X-linked inheritance

In X-linked inheritance, a mutated gene is located on the X chromosome, and the phenotype is determined by the gender of the individual (Figure 32.3). The genes located on the sex chromosomes, X and Y, are equally important in the developing fetus as the autosomes. Women have two X chromosomes and men have only one. However, the Lyon hypothesis explains that embryonic cells inactivate one X chromosome soon after conception and both men and women only have one functionally

Table 32.3 Definitions

Genotype	Normal or abnormal sequence of a particular gene
Phenotype	Clinical manifestation of a gene: normal or abnormal
Genetic heterogeneity	Similar clinical phenotype produced by different genetic mechanisms
Variable expressivity	Differences in clinical presentation within the same disorder
Penetrance	Probability derived from population studies that a specific genotype will be expressed
Pleiotropy	Multiple phenotypic effects from different mutations in a single gene

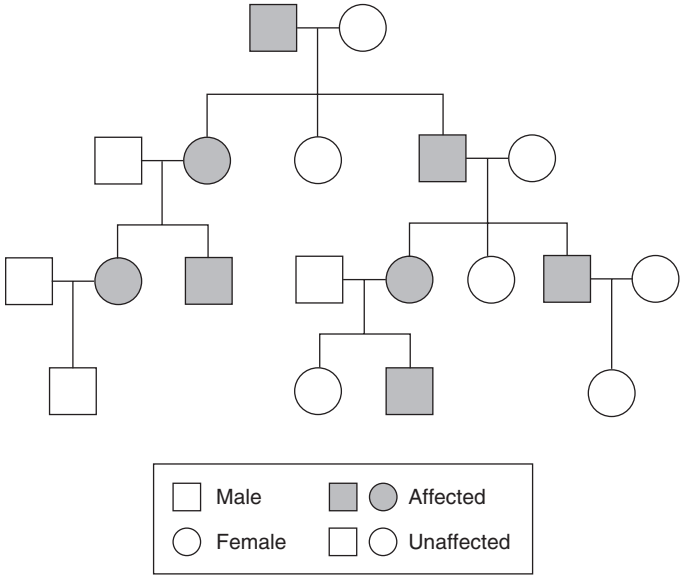

Figure 32.1 Autosomal dominant traits: vertical transmission (disorder may be present in more than one generation). Males and females are affected equally. An estimated 50% of offspring who are born to affected individuals can either have the condition or be predicted to have the condition. The risk of recurrence in the offspring of an affected individual is 1 in 2 (1/2) or 50%.

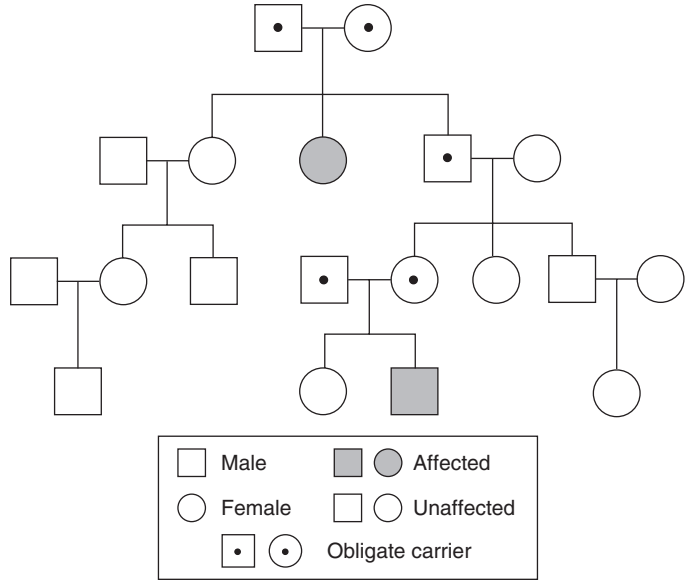

Figure 32.2 Autosomal recessive traits: transmission is horizontal, multiple siblings may be affected, but parents are unaffected as obligate carriers. In families where there is consanguinity, the risk for an autosomal recessive disorder is increased, depending on how closely related the parents are. Males and females tend to be affected in equal numbers. When two parents are obligate carriers, the risk for recurrence is 1 in 4, or 25% with each pregnancy.

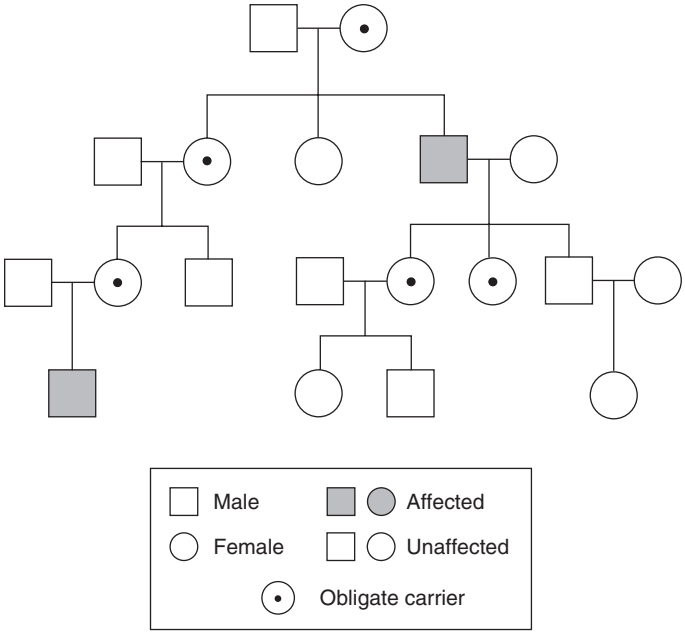

Figure 32.3 X- linked diseases. In an affected family, males are affected more frequently than females. Male-to-male transmission is not apparent. Detecting female carriers within a family may be difficult, as not every carrier will give birth to an affected son. All female carriers have a 1 in 2, or 50% risk of either having an affected boy or a female carrier. An affected male will uniformly transmit the mutated X chromosome to all his daughters, making them all obligate carriers.

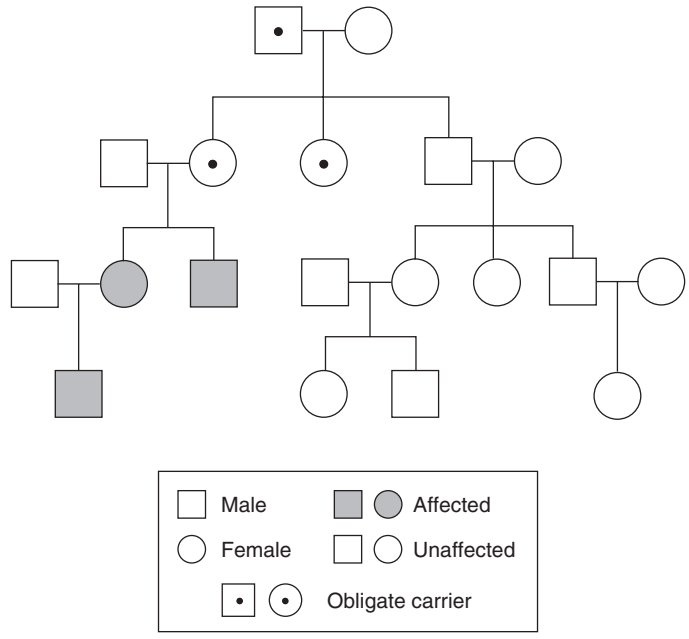

Figure 32.4 Anticipation phenomenon. Repetitive sequences, commonly triplicate repeats, are at risk for expansion in subsequent generations. Disease phenotype occurs after a 'threshold' of repeats is achieved.

active X chromosome. The Barr body, or the inactivated X chromosome, usually lies near the nuclear membrane, and can be identified during interphase in the cell cycle. Usually this inactivation is random, and individuals with more than two X chromosomes have multiple Barr bodies. Sometimes, however, a female may be affected due to 'poor lyonization,' or a predominant inactivation of the normal X chromosome.

Anticipation phenomenon

Anticipation (Figure 32.4) occurs when areas of repetitive sequence expand in size during subsequent generations. Myotonic dystrophy, fragile X syndrome, and Huntington disease are all examples of conditions caused by this mechanism.

Evaluation of the dysmorphic child

An in-depth physical examination and family and antenatal history are essential components of a genetic evaluation. The dysmorphic features and objective measurements should then be compared against a normal examination, within the context of how aberrancy in developmental embryology can contribute to phenotype. Based on these evaluations, radiographic and laboratory testing specific for a possible diagnosis may be considered. This testing may be cytogenetic (karyotype), molecular (fluorescence in situ hybridization (FISH)-based, or a DNA-based), or a biochemical analysis (acylcarnitine profile). Additionally, input from other specialty consultations such as ophthalmology or neurology may be critical. The clinical, familial, and laboratory-based studies *en total* hopefully provide for a unifying diagnosis that may allow for both a clinical plan for the particular child and possible genetic counseling for the family.

Autosomal dominant inheritance renal disorders

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder characterized by cysts in kidneys, liver, pancreas, arachnoid membrane, and seminal vesicles. Intracranial aneurysms, dolichoectasias, and cardiac manifestations (dilated aortic root, aneurysm, and mitral valve prolapse) are also common. Renal manifestations can include pain, hypertension, nephrolithiasis, and renal insufficiency. Approximately 50% of individuals who carry the diagnosis develop end-stage renal disease (ESRD) by 60 years of age.[6]

Prevalence of ADPKD is estimated at 1:400 to 1:1000.[6] Mutations in polycystin 1 (*PKD1*) on chromosome 16p13.3-p13.1 account for 85% of patients and correlate with a more severe phenotype. The remaining 15% of patients have mutations in polycystin 2 (*PKD2*), located on chromosome 4q21-q23. Commercial testing for both gene mutations is available for clinical use. All patients with ADPKD develop cystic kidneys, some of which are noted in utero. However, there is variability within families, which may be explained by modifier genes.[7] A microdeletion encompassing the *PKD1* locus and the tuberous sclerosis locus (*TSC2*) has also been reported, and these patients demonstrate severe renal manifestations at birth, along with the additional manifestations of tuberous sclerosis.[8]

Branchio-oto-renal syndrome

Branchio-oto-renal (BOR) syndrome, also known as Melnick–Fraser syndrome, is characterized by the presence of branchial arch remnants and results in cysts or fistulae, hearing loss (sensorineural, conductive, or mixed) due to inner, middle, or outer ear malformations, and a range of renal malformation from mild dysplasia to agenesis.[9] This diagnosis, as well as branchio-oto (BO) syndrome, appears to be caused by mutations in the *EYA-1* gene on chromosome 8q13.3.[10] *EYA-1* is expressed in the metanephric cells of the developing kidney, around the newly divided ureteric branches.[11] Recognizable mutations are found in only 40% of patients with a clinical diagnosis, and speculation for additional loci are ongoing.[12]

CHARGE syndrome

The acronym CHARGE refers to coloboma (C) of the iris and/or retina, heart (H) malformations, atresia choanae (A), growth retardation (R), genital abnormalities (G), and ear abnormalities and/or deafness (E). Specific renal findings include horseshoe kidneys and hydronephrosis, in addition to genital abnormalities such as cryptorchidism and microphallus. Mutations in the *CHD7* gene, a transcriptional regulatory protein, have been recently reported in 10 of 17 patients with this syndrome.[13] It is unclear if these are the only gene defects involved in the pathogenesis of this disorder.

Denys–Drash syndrome

Mutations in the Wilms' tumor 1 (*WT1*) on chromosome 11p13 show genetic pleiotropy. A number of clinical disorders result from mutations in the *WT1* gene, including the constellation of pseudohermaphroditism, nephropathy, and Wilms' tumor, or Denys–Drash syndrome (DDS).[14] The renal disease in DDS is characterized by diffuse mesangial sclerosis with subsequent renal failure, often by 3 years of age or earlier.[15] The severity of nephropathy at an early age should prompt the examiner to consider a karyotype, if phenotypically female, and the diagnosis is confirmed if the karyotype is male (46,XY). Ambiguous genitalia, hypospadias, cryptorchidism, or hypoplastic labia are also common findings in DDS.[16] The risk for development of Wilms' tumor appears to be dependent on the location and type of mutation.[17] Bilateral tumors occur more frequently in truncation mutations, especially those at the 5′ end of the gene.

Hajdu–Cheney syndrome

Acro-osteolysis with osteoporosis and changes in skull and mandible, or Hajdu–Cheney syndrome, is a rare autosomal dominant condition. Its molecular basis has not yet been defined. Along with osteopenia, these children have significant dysmorphism, hirsutism, midfacial flattening, and short stature. Genitourinary manifestations can include cryptorchidism and hypospadias. Additionally, renal enlargement with cortical and medullary cystic changes, with or without functional renal impairment, have been reported.[18]

Hemifacial microsomia (Goldenhar syndrome; facioauriculovertebral sequence)

Hemifacial microsomia (Goldenhar syndrome), or facioauriculovertebral sequence, has a variable phenotype, but generally involves the abnormal development of tissue originating from the first and second branchial arches. The usual findings include facial asymmetry with malar, mandibular, and maxillary hypoplasia and facial dysmorphia that involves the eyes and ears, and vertebral anomalies. Conductive hearing loss may be noted. Cleft palate and branchial arch remnants may also be present. Visceral involvement can include cardiac and cerebral malformations. Renal ectopia, agenesis, and dysplasia have also been noted. Most cases are sporadic and are postulated to occur via autosomal dominant mutation, but environmental influences, such as vascular insufficiency, diabetes may be involved.[19] Alternately, polygenic inheritance has also been suggested.[20] Linkage to chromosome 14q32 has been proposed, but no correlation to a specific gene has been established.[21]

Nail-patella syndrome

The usual triad of findings in this diagnosis includes pathologic changes in nailbeds, elbows, and knees. Nailbeds may be hypoplastic or absent, and often have triangular lunulae. Patellae may be absent or malformed, and are often asymmetric in their malformation. The elbows often demonstrate extension and rotation abnormalities. The finding of iliac horns on pelvic radiographs is considered pathognomonic for the diagnosis.

Mutations in the lim homeobox transcription factor 1 β (*LMX1*) gene are causative of nail-patella syndrome,[22] and molecular testing detects mutations in about 85% of patients. Renal pathology occurs in about 30–50% of patients, and usually presents with proteinuria that may also be accompanied by hematuria. Nephritis can also be present. About 5% of patients evolve into chronic renal failure.[23] However, renal involvement

tends to be intermittent, and may not be progressive. Additionally, dental, ophthalmologic, and vascular complaints have also been reported. [24]

Von Hippel–Lindau syndrome

The renal manifestations of Von Hippel–Lindau (VHL) syndrome include renal parenchymal cysts and renal cell carcinoma. Additional associations of VHL syndrome include hemangioblastomas of the brain, spinal cord, or retina; pheochromocytoma; and endolymphatic sac tumors. Mutation analysis of the VHL gene, located on chromosome 3p26-p25, detects nearly 100% of patients.[25] This gene encodes a tumor suppressor gene and genotype/phenotype correlations have helped create four subcategories of VHL syndrome.

Autosomal recessive inheritance renal disorders

Autosomal recessive polycystic kidney disease

The prevalence of autosomal recessive polycystic kidney disease (ARPKD) is much less than ADPKD, and is reported at between 1:10 000 and 1:20 000 of the population.[26] A majority of patients with ARPKD present either in utero, or in the neonatal period with enlarged echogenic kidneys and poor cortical medullary differentiation on ultrasound evaluation. Liver abnormalities such as hepatomegaly and dilated intrahepatic biliary ducts may also be present, although not always at birth. Mutations in the *PKHD1*, located on chromosome 6p.21 gene are causative of ARPKD.[27] The gene product appears to have many different isoforms made from alternative transcripts. Allelic heterogeneity is attributed to the variability in severity of presentation. The earliest manifestation of ARPKD can be detected in prenatal ultrasound. Almost half of the children who present in infancy also have liver disease that is characterized by hepatic fibrosis. The dominant cause of death during early infancy is due to pulmonary hypoplasia, related to the oligohydramnios commonly seen during pregnancy. Over half of children with ARPKD have ESRD within the first decade of life.

Bardet–Biedl syndrome (Laurence–Moon–Biedl syndrome)

Patients with Bardet–Biedl syndrome (BBS), or Laurence–Moon–Biedl syndrome, have clinical findings of truncal obesity, postaxial polydactyly, diabetes mellitus, mental retardation, retinitis pigmentosa, genital hypoplasia, and renal dysfunction. The renal concerns are ultimately responsible for the morbidity associated with this disorder, although not all progress to end-stage renal failure. Mutations in 1 of 5 known genes may cause BBS, although 7 putative loci have been identified. However, it is currently believed that the presence of a third mutation in one of the other genes may have a significant impact upon phenotype (triallelic inheritance).[28,29]

Cystinosis

Mutations in the lysosomal cystine transporter gene, cystinosin (*CTNS*), located on the short arm of chromosome 17 are causative for this autosomal recessive disorder.[30] This integral membrane protein is highly expressed in kidney, pancreas, and skeletal muscle. The natural course of disease usually includes hypothyroidism, Fanconi syndrome with renal tubular acidosis, and progression to chronic renal failure. Photophobia and retinopathy, diabetes, myopathy, and CNS (central nervous system) complications due to calcifications are also seen in long-standing disease.

An estimated incidence for cystinosis of 1:100 000 to 1:200 000 of the population has been reported, with a higher prevalence within Quebec and Brittany due to a Celtic-originated founder effect. The most common mutation involves a 57 kb deletion.[31] More severe mutations are responsible for the two nephropathic forms of the disease. The infantile form is commonly diagnosed within 6–18 months of age due to growth retardation and sequelae of renal tubular damage. The juvenile form is often diagnosed between 10 and 12 years of age due to glomerular damage and chronic kidney disease. An adult form consisting mostly of ocular pathology without any renal involvement is caused by mild mutations within the *CTNS* gene.

Diagnosis of cystinosis is established by biochemical analysis of the lysosomal enzyme (in leukocytes), or molecular analysis for the mutation of the affected genes, which is available for research purposes at this time. When tissue biopsies (e.g. renal biopsy, bone marrow) samples are obtained, the pathologist should be alerted to the possibility of cystinosis so that the slides are appropriately treated to preserve cystine crystals for diagnostic purposes.

Treatment with cysteamine helps to reduce the lysosomal accumulation of cystine in this disease. Such a treatment has been able to decrease many of the complications caused by cystine crystallization, and can delay the onset of ESRD.

Cystinuria

Cystinuria was one of the four original inborn errors of metabolism described by Garrod.[32] Mutations in the *SLC3A1* (solute carrier family 3) gene located on the short arm of chromosome 2 cause cystinuria type 1.[33] This gene encodes for the heavy subunit of a renal amino acid transporter, and is highly expressed in kidney and intestinal epithelial cells. Whereas individuals homozygous for the mutations demonstrate excessive urinary excretion of dibasic amino acids cystine, lysine, arginine, and ornithine, heterozygous individuals have normal urine amino acid profiles.

Prior to the identification of the genes responsible for this disease, three types of cystinuria were described based on

differences in parental and affected urine amino acid excretion. What was initially termed as type 3 disease was later found to be caused by mutations in the *SLC7A9* gene, coding for the light subunit of the renal amino acid transporter, located on chromosome 19.[34] The incidence is high in Libyan Jews, with a founder effect originating from either an Iberian or Portuguese ancestor.

The present explanation for the different clinical presentations is biallelic inheritance, where individuals with mutations in the *SLC7A9* gene, either homozygous or heterozygous, have significantly elevated urinary cystine levels, but only normal or mildly absent transport within intestinal epithelia. Individuals heterozygous for mutations in both *SLC3A1* and *SLC7A9* have a more mild presentation that falls between the homozygous patients. In general, treatment focuses upon increasing cystine solubility and utilizes urine alkalization and chelation agents such as pencillamine.

Bartter syndrome

Bartter syndrome is a multigenic disorder characterized by renal tubular dysfunction that manifests as hypokalemia, hypochloremia, metabolic alkalosis, and hyperreninemia amidst normal or low blood pressure. These patients have large urinary losses of sodium, potassium, and chloride, and can present with polyuria, polydypsia, constipation, and concerns for volume depletion.

Neonatal Bartter and classic Bartter syndrome can have non-specific prenatal findings, such as preterm labor and polyhydramnios. Amniotic fluid analysis may show high chloride levels in the context of normal concentrations of sodium, potassium, calcium, and prostaglandin E_2. Postnatal complications include growth retardation, life-threatening dehydration, muscle weakness and cramps, mild dysmorphism, and developmental delay.

Molecular studies in type I Bartter syndrome (neonatal) have shown mutations in the sodium chloride/potassium chloride cotransporter gene (*SLC12A1*) located on chromosome 15 in some patients.[35] Patients with type 2 Bartter syndrome (neonatal) have shown mutations in the *ROMK* gene (*KCNJ1*) on chromosome 11.[36] Type 3, or classic Bartter syndrome, is caused by a mutation in chloride channel B gene (*CLCNKB*).[37] Type 4 Bartter syndrome, associated with sensorineural deafness, results from either mutations in the Barttin (*BSND*) gene,[38] or simultaneous mutations in chloride channel genes encoded by *CLCNKA*[39] and *CLCNKB*,[37] all located on the distal portion of chromosome 1p.

Congenital nephrotic syndrome type 1 (Finnish type)

Frameshift mutations in the nephrin gene most commonly account for congenital nephrotic syndrome type 1 or Finnish type of congenital nephrotic syndrome (*NPHS1*).[40] Proteinuria occurs in utero and clinical presentation consists of severe nephrotic syndrome within the first few weeks after birth. Nephrotic syndrome is not responsive to steroid therapy. The gene for nephrin is located on chromosome 19q13.1 and encodes a transmembrane protein that appears to be related to the immunoglobulin family of cell adhesion molecules. The protein appears to be important for the normal formation of slit diaphragm and foot processes.[41] There is a high rate of maternal toxemia during affected pregnancies, and elevated α-fetoprotein levels in amniotic fluid have been used to support a diagnosis during pregnancies of at-risk families.[42] A founder effect with a newly distinct mutation is common amongst the old-order Amish families in Pennsylvania.[43]

Congenital nephrotic syndrome type 2

Positional cloning identified the gene podocin on chromosome 1q that is responsible for congenital nephrotic syndrome type 2.[44] Podocin is an integral membrane protein that appears to play an important role in the establishment of the glomerular filtration barrier. Absence of normal protein results in nephrosis. Koziell et al evaluated both podocin and nephrin mutations in a Finnish population with *NPHS1*, and found mutations in both genes, suggesting the mutations in podocin may act as a modulator to normal nephrin function.[45]

Smith–Lemli–Optiz syndrome

This disorder is characterized by scaphocephaly, ptosis with epicanthi, microcephaly, and 2–3 syndactyly of the toes. Other dysmorphia and malformations, such as congenital hip dislocation and subluxation, stippled bone epiphyses at birth, eczema and photosensitivity, and lung and cardiac malformations can also be seen. Genital abnormalities are more common in males and can include cryptorchidism, hypospadias, and ambiguous genitalia. Developmental renal manifestations include agenesis of one or both kidneys, cystic lesions, or hydronephrosis.[46] Mutations in the Δ7-dehydrocholesterol reductase gene on chromosome 11q12-q13 are causative, and clinical diagnosis may be confirmed by biochemical analysis of 7-dehydrocholesterol levels in serum.[47] The enzyme is important in the sterol synthetic pathway, whose products are essential for the developing embryo and for maintenance of normal cell physiology.

Smith–Lemli–Opitz syndrome is considered to be the first inborn error of metabolism shown to result in malformations.[48] Cognitive defects can vary; mental retardation can be severe and is a consistent finding. Mild presentations have been identified that correlate with compound heterozygosity from less classic mutations.[49] There appear to be additional modifiers of phenotype, some via maternal environment during pregnancy.[50] Presently, treatment is supplementation of diet with high cholesterol-containing foods such as egg yolks.[51]

Meckel–Gruber syndrome

Congenital renal dysplasia and CNS abnormalities, along with postaxial polydactyly, are the hallmarks of Meckel–Gruber

syndrome. There is wide variability in presentation, with significant debate as to the minimum dysmorphic features and malformations necessary to constitute a diagnosis.[52] The most common CNS malformation is encephalocele, and hepatic dysplasia can also be present. Three identified loci and two genes are felt to be involved, although mutation analysis of *MSK1* and *MSK2* are only available on a research basis.

X-linked inheritance renal disorders

Alport syndrome

The constellation of microscopic hematuria, sensorineural deafness, and ocular abnormalities, particularly anterior lenticonus, is suggestive of the diagnosis of Alport syndrome.[53,54] Immunohistochemical staining of renal biopsies from affected individuals demonstrates poor or absent staining for α_3, α_4, and α_5 (type IV) collagen in the glomerular basement membrane. Similar staining on skin fibroblasts has also demonstrated abnormalities in the α_5 (type IV) collagen. Mutations in three collagen type IV genes (*COL4A3*, *COL4A4*, and *COL4A5*) correlate with the clinical diagnosis. However, 80% of mutations in *COL4A5* demonstrate X-linked inheritance,[55] whereas about 15% of mutations found in either *COL4A3* or *COL4A4* are usually associated with autosomal recessive inheritance or autosomal dominant disease. A thorough family pedigree is imperative to try and distinguish between types, for genetic counseling and prospective management.

The differential diagnosis includes Fechner/Epstein syndrome, an autosomal dominant syndrome with clinical features of thrombocytopenia, hereditary nephritis, sensorineural deafness, and cataracts. Mutations in the non-muscle myosin heavy chain 9 are causative, and ESRD has been reported.[56,57]

Lowe syndrome (oculocerebrorenal syndrome)

Lowe syndrome (oculocerebrorenal syndrome) is characterized by the clinical features of cataracts and/or additional eye findings, mental retardation, vitamin D-resistant rickets, and renal Fanconi syndrome (metabolic acidosis, aminoaciduria, proteinuria, and hyperphosphaturia).[58] Subsequent studies have also shown detectable abnormalities, such as aminoaciduria after ornithine loading,[59] and cataracts in maternal obligate carriers. Additional molecular analysis demonstrated mutations in the gene encoding the enzyme phosphatidylinositol 4,5-bisphosphate 5-phosphatase in male patients with corresponding clinical features.[60] The gene is now called *OCRL1*, and enzyme analysis in fibroblasts or mutation analysis is clinically available. Treatment is based on an individual patient's clinical symptoms. Patients with proximal renal tubular disease are supplemented with oral potassium bicarbonate and/or citrate for control of acidosis and hypokalemia. Vitamin D and phosphate may be helpful to control bone disease.

Fabry disease (α-galactosidase deficiency)

Alpha-galactosidase A deficiency, or Fabry disease, is a lysosomal storage disorder where enzyme deficiency results in accumulation of globotriaosylceramide (GL-3), a sphingolipid.[61] Diagnosis is confirmed by biochemical analysis of the enzyme's activity in leukocytes. DNA mutation analysis, best utilized for identification of carrier females, is also available through commercial laboratories.

GL-3 accumulates in vascular tissue. Cardiac, dermatologic, cerebral, and renal manifestations are common. Diagnosis may be suspected with a combination of any of the following complaints: angiokeratoma and hypohidrosis, congestive heart failure, cardiac valvular disease, hypertension, anemia, stroke, and paresthesia. Women can present with milder presentation due to poor lyonization. Corneal dystrophy may be seen in both female carriers and affected males. Renal failure and isosthenuria are also common.

In the past, patients with renal disease have often progressed to ESRD. However, enzyme replacement therapy has been shown to be a successful in decreasing plasma levels of GL-3.[62] Preparations of recombinant enzyme (agalsidase-β from Chinese hamster ovary cells; agalsidase-α from human fibroblasts) have proven effective in clinical trials, and have shown decreased GL-3 levels in blood. Long-term studies are presently ongoing, but it is hoped that replacement therapy will decrease known complications, including renal manifestations.

Mitochondrial inheritance

Children and adults with mitochondrial based diagnoses may have mutations in either the eukaryotic genome or the mitochondrial genome. The mitochondrial genome is transmitted only via the maternal lineage (Figure 32.5). Mutations in the mitochondrial genome can also affect kidney function. Compared to the estimated number of genes carried on the eukaryotic genome, the mitochondrial genome is small. However, they often work in complexes with genes located on eukaryotic chromosomes. Mitochondrial encoded genes are generally involved in energy production and, therefore, mutations that affect function are most commonly seen in tissues which have the highest energy requirements, such as the heart and cerebrum, and can result in primary lactic acidosis.

Disease-causing mutations are often important for oxidative phosphorylation or tRNA utilization. Mitochondria are passed via the mother, and there may be more than one population (mutated vs non-mutated) in each cell. In order for the phenotype to be apparent, the number of mitochondria per cell with disease-causing mutations must exceed a certain threshold level. This number may vary in an individual person by tissue, such that for a specific family member, cardiac tissue may be more affected than cerebral tissue or pancreatic tissue. Progressive encephalopathy, cardiomyopathy, lactic acidosis, renal tubular acidosis, nephrotic syndrome, and stroke-like

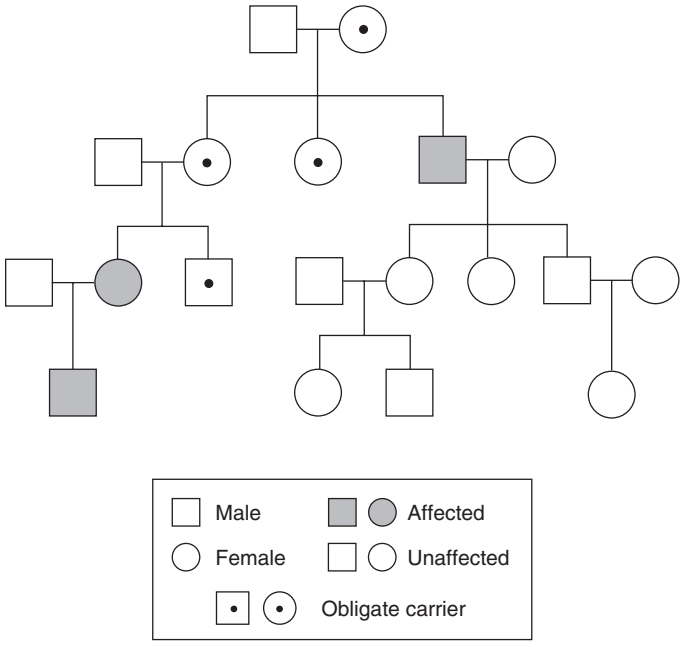

Figure 32.5 Mitochondrial inheritance. The mitochondrial genome is passed via the ovum, and therefore via the maternal lineage.

episodes are some of the phenotypes seen with mitochondrial mutations.[63,64]

Concluding remarks

The ability to make a specific diagnosis can have an enormous impact upon treatment and anticipation of additional complications. Any child with unexplained nephropathy warrants an aggressive evaluation, with consideration for imaging, non-routine laboratory testing (i.e. urine amino acids or lysosomal storage enzymes), and evaluation for dysmorphism and developmental delay. Advances in the field of genetics that contribute to diagnosis and therapy are ongoing. As the dialogue progresses, these advances will be important contributions to patient care, and as essential as the dialogue itself.

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33 Obstructive uropathy

Robert L Chevalier

Obstructive uropathy is one of the most important identifiable causes of renal insufficiency in infants and children.[1] The majority of cases of obstructive uropathy in the pediatric population are the result of congenital malformations of the urinary tract, accounting for 1 of 1000 live births.[2] Although it would seem that a definition of obstructive uropathy would be straightforward, there is no general agreement regarding criteria. What is 'critical' obstruction of the urinary tract? What is the degree of obstruction that impairs renal growth and long-term renal function? Using these paradigms, Peters has defined obstruction as 'a condition of impaired urinary drainage, which, if uncorrected, will limit the ultimate functional potential of a developing kidney'.[3] Although this definition takes into account the relationship between renal function and renal development, it does not provide a useful clinical benchmark to determine a critical degree of urinary tract obstruction in the fetus or infant. This chapter attempts to bring together the available experimental evidence and clinical experience to provide an approach to the fetus, infant, or child with obstructive uropathy.

Epidemiology

The incidence of ureteropelvic junction (UPJ) obstruction is 1 in 1500, and it is the most common cause of hydronephrosis detected prenatally.[4,5] The most common locations for congenital urinary tract obstruction are shown in Figure 33.1. Ureterovesical junction (UVJ) obstruction accounts for about 20% of cases of neonatal hydronephrosis. Although the incidence of posterior urethral valves (PUV) is only 1 in 5000,[6] since both kidneys are involved, it is the lesion for which intervention is potentially most urgent.

Pathophysiology

Renin–angiotensin involvement

The renin–angiotensin system clearly modulates the development of the collecting system, and mice with mutations of the angiotensin receptors develop anomalies of the kidneys and urinary tract similar to those in man.[7] Although clinical studies have suggested an association of urinary tract anomalies with mutations in components of the renin–angiotensin system in some populations, this has not been confirmed in others.[8]

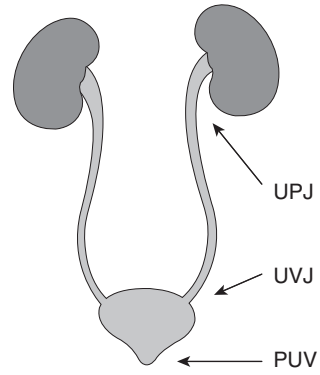

Figure 33.1 Location of most common sites of congenital urinary tract obstruction. UPJ, ureteropelvic junction; UVJ, ureterovesical junction; PUV, posterior urethral valves. (Reproduced with permission from Chevalier.[9])

Genes in obstructive uropathy

Although a number of candidate genes have been proposed to account for maldevelopment of the urinary tract, none have yet been shown to play a central role in the genesis of the common lesions of obstructive uropathy. It is likely that, as with most congenital anomalies, multiple genes may be involved, in addition to environmental factors affecting the developing embryo and fetus. Unlike some congenital renal anomalies (such as renal agenesis), the relative contribution of disordered morphogenesis to the long-term outcome of children with obstructive uropathy is shared with the consequences of obstructed urine flow on the developing or maturing kidney. It is the latter that may be amenable to medical or surgical intervention.

Effects on renal development

Compared with the adult kidney, the developing kidney is highly susceptible to injury from obstruction to urine flow.[9] Much of our understanding of the impact of urinary obstruction on renal development and function comes from experimental models. A number of models have been investigated, and each has its advantages and disadvantages. Since the lesions of obstructive uropathy develop in fetal life, the consequences of surgical obstruction of the ureter or urethra have been studied in the fetal sheep.[10] The limitations of this model are the expense involved in the care of large animals and the challenge

of measuring renal function in the fetus. Over the past two decades, much has been learned from studies of unilateral ureteral obstruction (UUO) in the developing rat or mouse.[11] As shown in Figure 33.2, whereas nephrogenesis in man is complete before birth, nephrogenesis in the rat proceeds after birth. Surgical obstruction of the ureter in the neonatal rat or mouse is therefore analogous to ureteral obstruction in the midtrimester human fetus.

Temporary complete UUO in the neonatal rat impairs growth of the obstructed kidney, which is directly correlated with the duration of obstruction (Figure 33.3).[12] This suggests that delay in the relief of severe obstruction can permanently impair the growth potential of the kidney. Chronic partial UUO in the neonatal rat also impairs renal growth, an effect that is dependent on the severity of obstruction (Figure 33.4).[13] There appears to be a critical reduction in ureteral diameter (65%), which if exceeded results in impaired renal growth. Since renal growth is a major determinant of long-term renal function, a better understanding of what constitutes 'critical' ureteral stenosis may permit the development of a better definition of clinically significant obstruction.

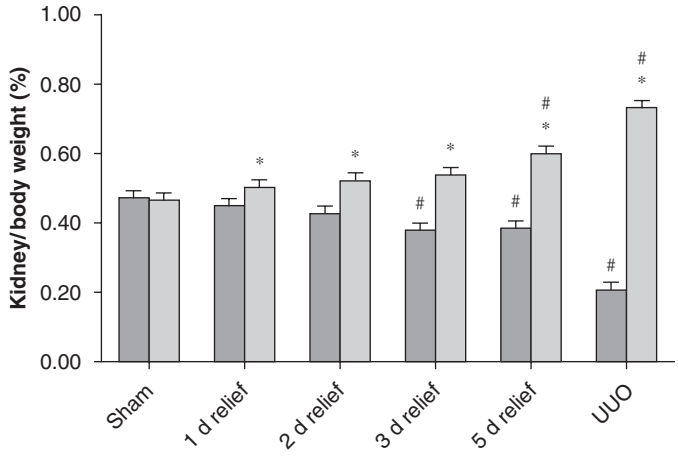

Figure 33.3 Kidney/body weight ratio of obstructed (black) and contralateral (white) kidneys of neonatal rats 28 days following sham operation, following relief of 1–5 days of unilateral ureteral obstruction (UUO), and following persistent complete UUO. *$p < 0.05$ vs UUO kidney, #$p < 0.05$ vs sham. (Reproduced with permission from Chevalier et al.[12])

Impact on renal growth

Chronic UUO delays maturation of all components of the nephron, from the glomerulus to the collecting duct, as well as the microvasculature and renal interstitium.[14] As a consequence of obstruction, there are also major hemodynamic changes, with profound renal vasoconstriction mediated by the renin–angiotensin system (already highly activated in the developing kidney compared with the adult).[15–20] Although the renal vasoconstriction is modulated by endogenous vasodilators such as prostaglandins and nitric oxide, the net balance favors

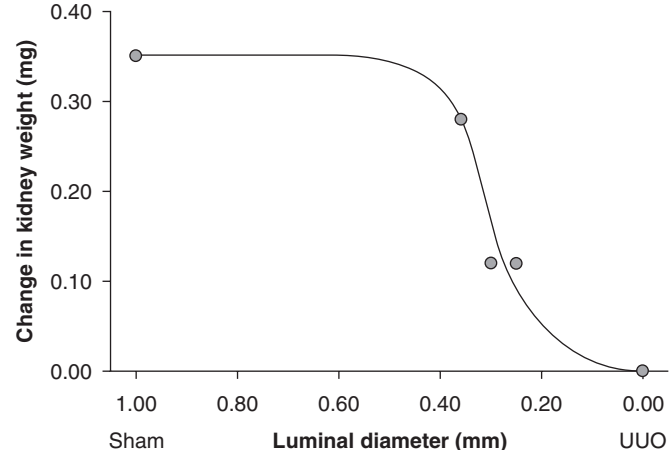

Figure 33.4 Interval renal growth as a function of ureteral obstruction between 14 and 28 days after operation. Each point represents the mean for the group. Complete unilateral ureteral obstruction (UUO) is represented by luminal diameter = 0.00, whereas sham operation is represented by luminal diameter = 1.00 mm. (Reproduced with permission from Thornhill et al.[13])

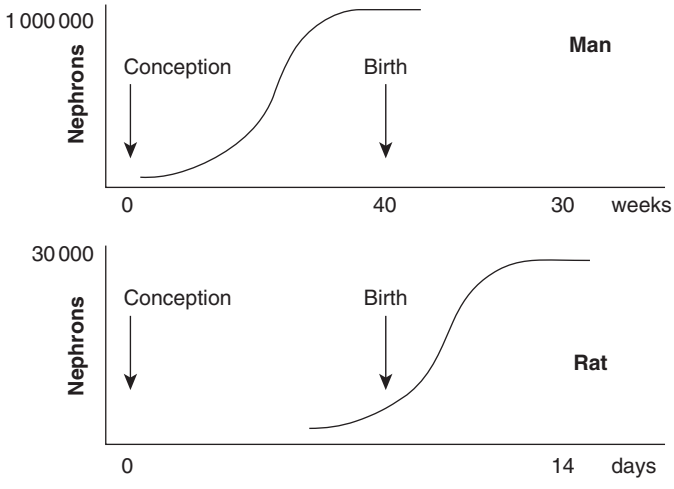

Figure 33.2 Nephrogenesis in humans (A) and rat (B). In humans, nephrogenesis takes place primarily in midtrimester gestation, with completion of nephron formation by the 34th week. In the rat, nephrogenesis begins toward the end of gestation, with most nephrons being formed during the first 2 weeks of postnatal life. (Reproduced with permission from Chevalier.[11])

vasoconstriction.[21,22] There is increased renin production by afferent arterioles, and an up-regulation of molecules induced by activation of the renin–angiotensin system.[18,23,24] These include the fibrogenic cytokine transforming growth factor-β_1 (TGF-β_1), discussed further below.[23]

Effects of tubulointerstitial tissue

The hallmarks of chronic severe obstructive uropathy are the development of tubular atrophy and interstitial fibrosis, both of which contribute significantly to impaired renal growth. It has

become clear that tubular atrophy results from progressive destruction of tubular epithelial cells by apoptosis, or programmed cell death.[25,26] Chronic partial UUO in the neonatal rat leads to apoptosis of epithelial cells in dilated collecting ducts, and the characteristic atrophic tubules with thickened basement membranes (Figure 33.5).[13] Stimuli leading to tubular apoptosis include mechanical stretch of epithelial cells in dilated tubules, as well as altered gene expression (Figure 33.6).[14,26–29] Renal tubular expression of epidermal growth factor (a survival factor) is reduced by UUO, whereas expression of TGF-β_1 (a proapoptotic factor) is increased by UUO.[14] The balance of survival and death signals is tipped in favor of cell death, leading to progressive loss of renal mass.[30]

Chronic UUO also has profound effects on the renal interstitium, leading to infiltration by macrophages and fibroblasts, which release cytokines such as TGF-β_1 (Figure 33.6 and 33.7). Activated macrophages and their products can induce both tubular apoptosis and progressive interstitial fibrosis (Figure 33.7).[31] This can involve the transformation of interstitial fibroblasts into myofibroblasts that express α-smooth muscle actin and release additional fibrogenic molecules (see Figure 33.6).[14] Most remarkable is the recent discovery that mechanical stretching of tubular cells and changes in the local production of growth factors, cytokines, and chemokines can lead to transformation of renal tubular epithelial cells to assume mesenchymal characteristics.[32,33] Tubular cells undergoing epithelial–mesenchymal transformation can differentiate into fibroblasts that augment the progression of interstitial fibrosis.[34] The multiple interacting processes depicted in Figure 33.6 are dynamic and activated by the persistence of significant urinary tract obstruction. A more thorough understanding of these interactions may lead to improved therapies for obstructive uropathy: by interfering with tubular apoptosis, macrophage infiltration, or epithelial–mesenchymal transformation. Once this process has progressed to tubular atrophy and extensive interstitial fibrosis, the impairment of renal growth becomes irreversible.

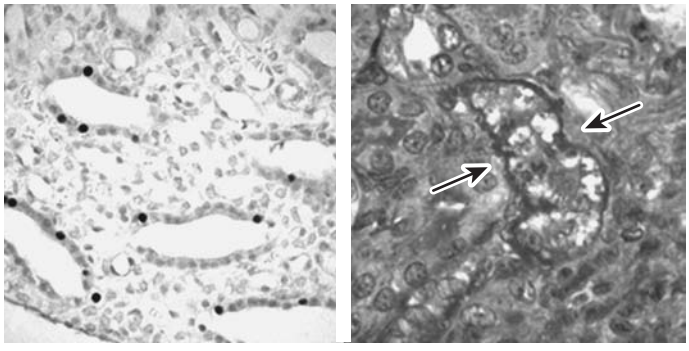

Figure 33.5 Kidney sections from neonatal rats following 14 days partial unilateral ureteral obstruction. (A) Dart-stained apoptotic nuclei in dilated tubules are identified by dUTP-biotin nick end labeling (TUNEL) technique. (B) Atrophic tubules are identified on PAS-stained sections by thickened tubular basement membrane (arrows). (Reproduced with permission from Thornhill et al.[13])

Nephron loss in urinary obstruction

Chronic UUO not only causes tubulointerstitial changes but also leads to loss of nephrons. Even temporary complete UUO during nephrogenesis or during nephron maturation can permanently reduce the number of nephrons in the obstructed kidney.[35,36] Chronic partial UUO in the neonatal rat also reduces nephron number, although the loss of nephrons takes place over a longer period of time.[13] As with any loss of renal mass, chronic UUO leads to compensatory growth of the opposite kidney. This 'counterbalance' is very finely tuned, and develops after even short periods of ureteral obstruction (see Figure 33.3).[12,37] Since the severity of urinary tract obstruction in clinical practice is usually unequally distributed between the

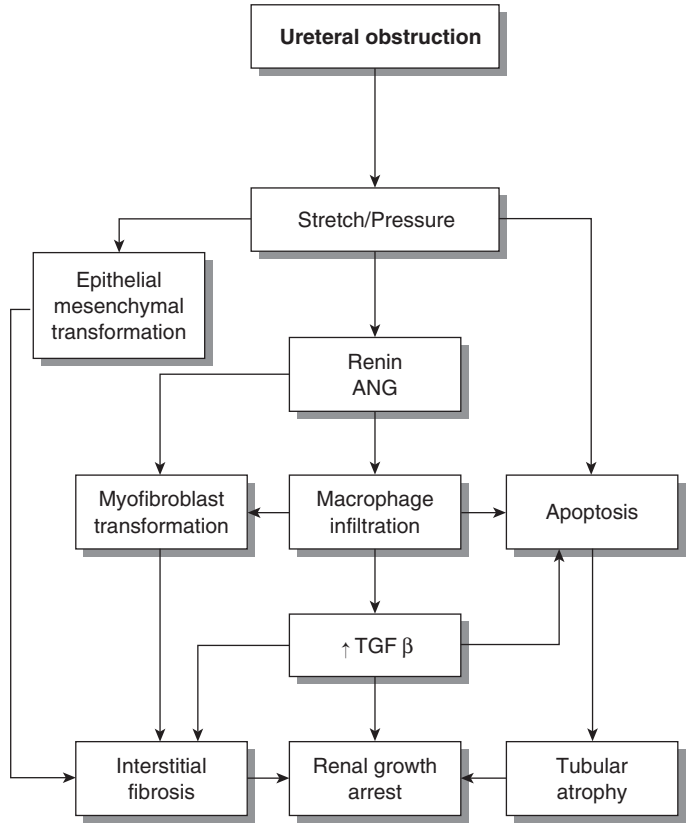

Figure 33.6 The cellular effects of chronic ureteral obstruction on the developing kidney. Ureteral obstruction results in dilatation of tubules, stretching tubular epithelial cells, and stimulating the local renin–angiotensin system, as well as transformation of epithelial cells into mesenchymal cells (including fibroblasts). Increased local production of angiotensin stimulates macrophage infiltration and transformation of interstitial fibroblasts into myofibroblasts. In addition, increased intrarenal production of transforming growth factor-β (TGF-β) promotes deposition of extracellular matrix (enhancing interstitial fibrosis), and stimulates tubular apoptosis. The mechanical stretch of tubular cells promotes their apoptosis, and infiltrating macrophages release compounds that also stimulate apoptosis. Tubular apoptosis, in turn, leads to tubular atrophy, which contributes to nephron loss. The combination of nephron loss and interstitial fibrosis lead to arrested growth of the kidney. ANG, angiotensin.

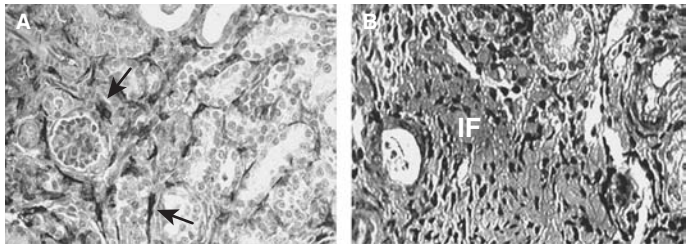

Figure 33.7 Kidney sections from neonatal mice following chronic unilateral ureteral obstruction. (A) Macrophage infiltration, with macrophages stained black (arrows). (Reproduced with permission from. Lange-Seperandio et al., 2002.[31] (B) Renal interstitial fibrosis (IF) identified by collagen staining using Masson trichrome stain. (Reproduced with permission from Fern et al.[88])

two kidneys, adaptive growth by the remaining nephrons may occur in both kidneys. Current limitations in detecting such adaptive growth lie in the relative lack of precision in imaging techniques, as well as in the measurement of differential renal function.[38]

Impact on tubular functions

Chronic obstructive uropathy leads to impaired tubular function that can have significant clinical implications. Down-regulation of sodium transporters and aquaporins, and distortion of the medullary architecture, contribute to limited renal concentrating capacity.[39,40] These factors contribute to the phenomenon of 'postobstructive diuresis' that often follows the relief of severe bilateral urinary tract obstruction (such as posterior urethral valves).[40] Since positive sodium balance is necessary for normal somatic growth in infancy, impaired growth is another consequence of reduced renal sodium reabsorption in obstructive uropathy.[41] Thus, infants may require sodium supplements to prevent volume contraction and to optimize somatic growth. Somatic growth may also be limited in obstructive uropathy by abnormal distal tubular potassium and hydrogen ion secretion consequent to type 4 renal tubular acidosis.[42] These tubular defects can lead to hyperkalemia and metabolic acidosis even with unilateral obstruction,[43] and may persist even after surgical relief of the obstruction.[44]

Clinical presentation and evaluation

Prenatal

Most cases of congenital obstructive uropathy are now detected by prenatal ultrasonography, usually performed between 16 and 20 weeks of gestation. Measurement of the anteroposterior diameter of the renal pelvis has been used as an index of the severity of hydronephrosis. The risk of clinically significant urinary tract obstruction is increased when the fetal renal pelvic diameter exceeds 6 mm at less than 20 weeks, 8 mm at 20–30 weeks, or 10 mm at more than 30 weeks of gestation.[45] However, it should be emphasized that basing the diagnosis of fetal hydronephrosis on renal pelvic dimensions can be misleading: not only is the reliability of the measurement operator-dependent but also the high urine flow of the fetus can cause relative distention of the pelvis just before fetal micturition, and normal dimensions following fetal voiding (even with a partially obstructed ureter). Thus, many cases of suspected fetal hydronephrosis are not confirmed on postnatal ultrasonography, causing unnecessary worry for the parents during the pregnancy. Equally important in prenatal diagnosis is the dilatation of renal calyces, with greater severity of calyceal dilatation indicating clinically significant hydronephrosis (Figure 33.8).[46] Additional information that should be gathered includes whether the lesion is unilateral or bilateral, whether the ureter is dilated, whether the bladder is dilated or thickened, and whether there are other organ system abnormalities. Not all cases of fetal hydronephrosis are the result of obstruction;

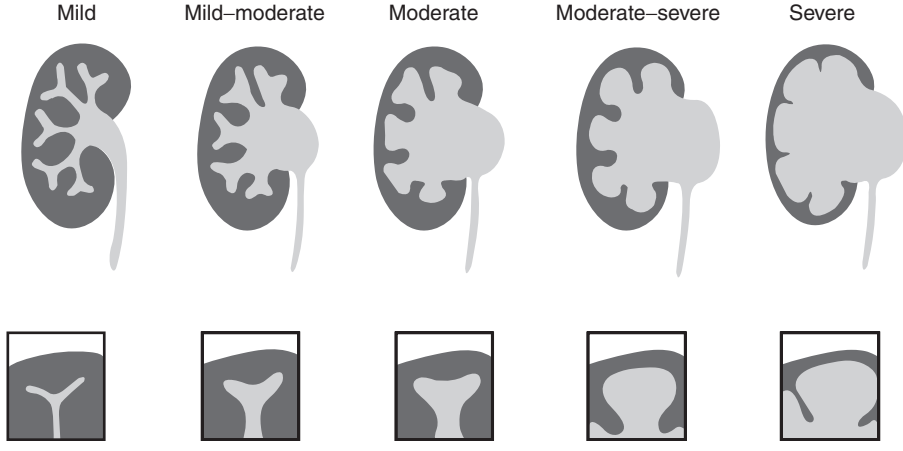

Figure 33.8 The appearance of progressive severity of hydronephrosis, including calyceal configuration. (Reproduced with permission from Peters.[46])

vesicoureteral reflux, megacalicosis, and renal cystic disease must also be considered.

The development of bilateral renal impairment in the fetus with bladder outlet obstruction (such as from PUV) has major consequences, not only for the urinary tract but also for pulmonary development. Severe oligohydramnios resulting from PUV leads to pulmonary hypoplasia that can be more life threatening in the immediate postnatal period than renal failure itself. An estimation of amniotic fluid volume is critical in the evaluation of any fetus with suspected renal or urinary tract anomalies. Further refinement has been attempted in predicting which fetuses with bladder outlet obstruction have a poor renal prognosis. Fetal urine sodium concentration is normally less than 90 mmol/L at 20–30 weeks gestation.[47] Higher fetal urinary sodium values are suggestive of abnormal tubular functions as a result of renal maldevelopment. Similarly, urine osmolality should be less than 200 mOsm/kg, and higher values are consistent with significant renal impairment.[47] The sensitivity and specificity of fetal urine chemistries are not ideal, however, and the results lack predictive value.[47] The measurement of fetal urinary amino acids appears to provide greater discrimination between grades of fetal renal impairment, although this approach has not gained widespread use.[48]

Postnatal

Obstructive uropathy should be suspected in any infant or child with a palpable abdominal mass. Signs may include flank pain, incontinence, urinary tract infection, or hematuria. Patients with imperforate anus, other organ system anomalies, or suspected syndromes should also be suspected of having obstructive uropathy.

The initial diagnostic study for these patients, or for any infant with a suspicious prenatal ultrasound, should be postnatal ultrasound of the kidneys, ureters, and bladder. Except for infants with suspected bladder outlet obstruction (who should have immediate imaging studies), ultrasonography should be performed in the well-hydrated infant after several days of age, to optimize the detection of hydronephrosis. Intravenous pyelography is indicated only in a rare circumstance in an older infant or child in whom anatomy may be needed to be better defined in preparation for surgical intervention. Diuretic renography is useful to determine the relative contribution of each kidney to total renal function, and the location of functional obstruction to urine flow. The study should be performed with a bladder catheter in place and, unless there is an urgent need (suspected PUV), should be delayed until the infant is several weeks of age (maturation of renal concentration significantly improves the quality of imaging).[49] Voiding cystourethrography is an additional study that can rule out vesicoureteral reflux (often present contralateral to UPJ obstruction) or PUV.

It needs to be emphasized that although the current combination of ultrasonography and renography provides useful information in the management of the infant with suspected obstructive uropathy, neither technique will determine conclusively whether or not the lesion should be surgically corrected, or when it should be done. As discussed below, this is a clinical decision that should involve the pediatric nephrologist, urologist, and radiologist.

Management

Prenatal management

Fetuses with unilateral hydronephrosis should have serial ultrasound examinations, but are not candidates for prenatal surgical intervention. Fetuses with bilateral hydronephrosis and oligohydramnios are at risk for the development of pulmonary hypoplasia. Prenatal intervention for PUV by the insertion of a catheter to divert fetal urine into the amniotic space has been reported from a number of centers, but the results have been largely disappointing, with a high incidence of displacement of the catheter, amnionitis, and fetal loss.[50,51] Moreover, even in fetuses with successful retention of the catheter through pregnancy and normal postnatal pulmonary function, long-term renal function may be poor.[50] This is probably due to the progression of renal maldevelopment in the first trimester, before the kidneys and urinary tract can be reliably identified by maternal sonography.

Postnatal management

The postnatal management of the infant with obstructive uropathy depends on the specific findings from the imaging evaluations described above. For the infant with unilateral UPJ obstruction, mild obstruction (without caliectasis) may be followed with sequential renal ultrasound examinations: many of these patients will undergo progressive spontaneous improvement of the obstruction.[52] For infants with moderate to severe UPJ obstruction, there is considerable controversy regarding the indications for early operative correction vs long-term observation.[52–55]

Based on the experimental data described above, the truly 'conservative' approach for the pediatric urologist is to consider early pyeloplasty to avoid ongoing renal damage.[56,57] The difficulties of subjecting infants to repeated ultrasound studies and diuretic renography should also be taken into account, and non-compliance with a rigorous schedule of imaging studies may lead to irreversible loss of renal function.[58] Although most pediatric urologists are reluctant to postpone surgical correction in infants with bilateral UPJ obstruction, Onen et al have advocated non-operative management with close follow-up during the first 2 years of life.[59] The significant risks resulting from inadequate compliance with very close follow-up in this group have been emphasized by Peters.[60]

For the infant with bilateral hydronephrosis, or any infant with suspected bladder outlet obstruction, a voiding cystogram should be obtained promptly. Once PUV are diagnosed, the bladder should be drained with a sterile 5 French feeding tube

and serial plasma creatinine concentration should be measured until it stabilizes. Many cases of bladder outlet obstruction are associated with vesicoureteral reflux, or with secondary ureteral obstruction due to ureteral dilatation and kinking. Pending complete radiologic evaluation, it is most prudent to treat infants with prophylactic antibiotics to minimize the development of urinary tract infection and septicemia. Oral amoxicillin, 10 mg/kg daily, should be used in the infant (unless there are specific contraindications). As noted above, infants undergoing surgical correction of obstructive uropathy may require increased sodium intake and/or alkali therapy to optimize growth.[61]

Long-term outcome

Most published studies of congenital obstructive uropathy are limited to several years follow-up. For children with stable mild to moderate UPJ obstruction, or even those undergoing pyeloplasty, few receive long-term follow-up care. Unfortunately, plasma creatinine concentration and urine protein excretion are relatively insensitive markers of progression of obstructive uropathy: abnormal values will develop only with significantly advanced renal disease.

For patients with bladder outlet obstruction, continued monitoring is particularly important. Most patients with PUV diagnosed in the perinatal period develop renal insufficiency by 10 years of age, despite surgical correction of the obstruction (Figure 33.9).[62]

Follow-up of infants and children with obstructive uropathy should include regular monitoring of blood pressure, urinalysis, urine culture, plasma creatinine concentration, and renal ultrasound (Table 33.1). Renal ultrasound permits an estimate of renal growth as well as the dimensions of the collecting system. In addition, monitoring the rate of growth of the normal contralateral kidney has been suggested as an index of functional impairment of the obstructed kidney as revealed by compensatory growth.[63,64] This reflects 'counterbalance', as shown in the animal model with varying duration of complete UUO (Figure 33.3).[12] It is important to emphasize that serial measurements are necessary to detect the subtle changes in renal dimensions over time.[65,66]

In addition to monitoring these patients, the family should also be counseled to maintain adequate hydration and sodium repletion (particularly in hot weather) in the affected patient. The use of nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), should be avoided.

Some studies have suggested that if the nadir plasma creatinine concentration falls below 0.9–1.2 mg/dl following surgical correction in infancy, the child is likely to avoid the development of renal failure.[67,68] However, there are few studies carried out over a 10-year period, and the rate of progression of congenital obstructive uropathy is often slower than that of glomerular disorders. As illustrated in Figure 33.10, a plasma creatinine concentration below 1 mg/dl does not guarantee preservation of renal function over longer periods. Even patients with UPJ obstruction develop glomerular sclerosis, which is consistent with hyperfiltration injury.[69,70] Pyeloplasty performed in patients with severe UPJ obstruction may not result in improvement or even preservation of existing nephrons and function.[71,72] Similar changes are found 1 year after release of temporary complete UUO in the neonatal rat.[38]

Parents of children with obstructive uropathy should be advised that, despite surgical intervention, renal structure and function rarely normalize completely, and that gradual progression is possible regardless of the time of diagnosis and treatment. Although patients with obstructive uropathy often suffer from urinary sodium wasting due to tubulointerstitial changes, children with intermittent complete obstruction of severe UPJ stenosis can develop hypertension.[73] With progressive interstitial fibrosis and glomerular sclerosis, hypertension can develop in any child with obstructive uropathy. Since hypertension

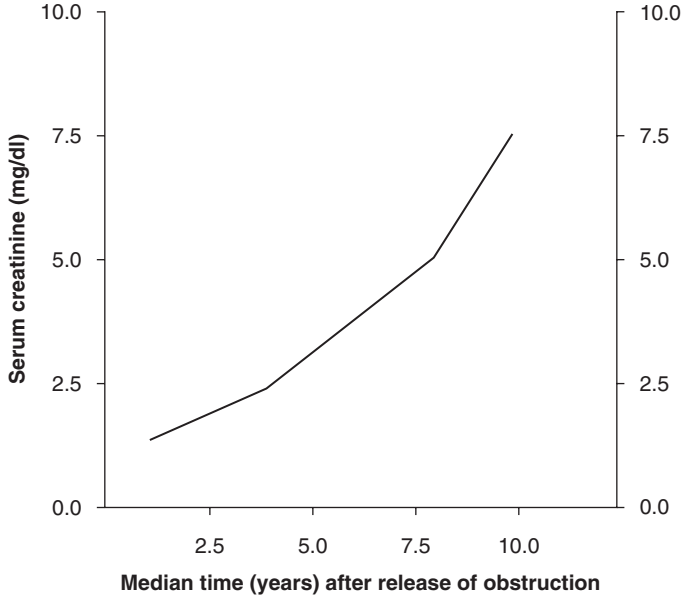

Figure 33.9 Serum creatinine elevation vs median time, in years, from nadir serum creatinine concentration after relief of posterior urethral valves. (Reproduced with permission from Roth et al. [62])

Table 33.1 Clinical principles of follow-up of congenital obstructive uropathy

Monitor blood pressure – avoid hypertension
Urinalysis
Urine culture – prevent urinary infection
Plasma creatinine concentration
Renal ultrasound
Avoid dehydration
Avoid use of NSAIDs

NSAIDs, non-steroidal anti-inflammatory drugs.

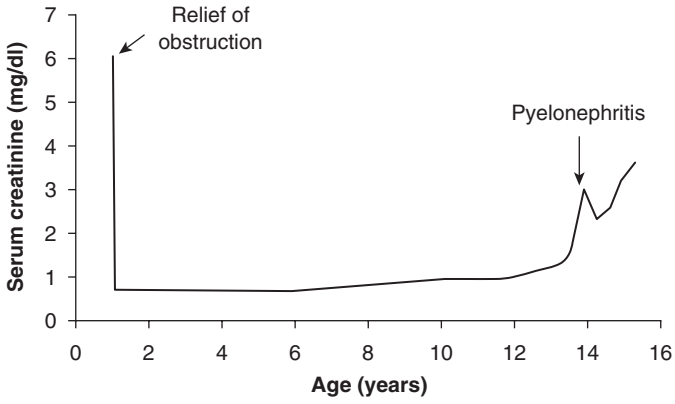

Figure 33.10 Serum creatinine concentration vs patient age, in years, for a child presenting with seizures at 1 year of age, and undergoing fulguration of posterior urethral valves (relief of obstruction). Serum creatinine remained below 1 mg/dl for a decade before the patient developed pyelonephritis, and creatinine increased acutely. Despite treatment of the infection, creatinine continued to increase, and the patient developed end-stage renal disease.

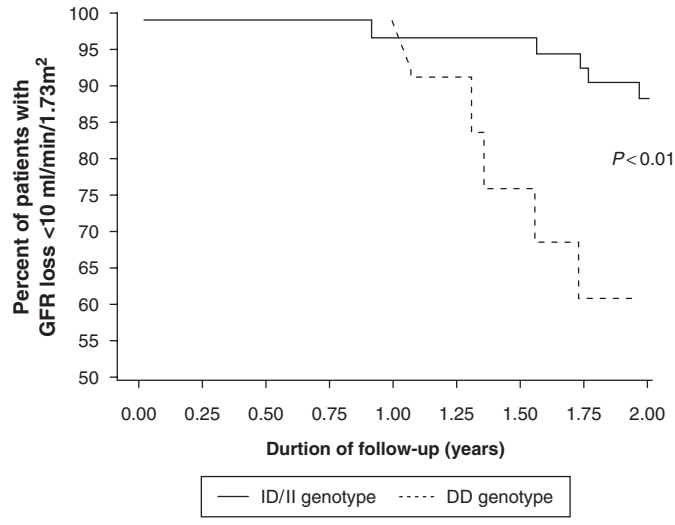

Figure 33.11 Renal 'survival' analysis in children with chronic renal failure due to renal malformations. During 2 years of follow-up, a loss of glomerular filtration rate (GFR) > 10 ml/min/1.73 m^2 was observed in 39% of patients with the ACE DD genotype, but only in 11% of patients with the ID or II genotype. (Reproduced with permission from Hohenfellner et al.[74])

itself is a major determinant of the progression of renal insufficiency, it is critical to monitor blood pressure and to treat hypertension aggressively.

There is mounting evidence that the patient's genotype is also a significant determinant of progression, and angiotensin-converting enzyme (ACE) gene polymorphisms can profoundly affect the rate of progression in individual patients (Figure 33.11).[74] It is also becoming clear that angiotensin, as well as hypertension, can contribute to proteinuria in progressive renal disease, and that proteinuria itself can aggravate glomerular and tubular injury (Figure 33.12).[75] Since the intrarenal renin–angiotensin system is highly activated in obstructive uropathy, inhibition of angiotensin by ACE inhibitors or angiotensin receptor blockers should have a salutary effect on both the hemodynamic and the fibrotic consequences of chronic urinary tract obstruction (Table 33.2). However, inhibition of angiotensin can impair normal renal development and maturation through the period of infancy, and should be used with great caution in the first 6 months of life.[76,77] Moreover, angiotensin inhibition can markedly reduce glomerular pressure in the neonate and infant.[78] Combined with its effect in reducing tubular sodium reabsorption, which is already impaired in obstructive uropathy, angiotensin inhibition can significantly reduce glomerular filtration rate.[79] Once again, caution must be exercised in the administration of these agents in children with obstructive uropathy.

Illustrative case

A representative case of PUV is illustrated in Figure 33.10. This patient was not diagnosed prenatally, and had recurrent episodes of vomiting and failure to thrive in infancy. At 1 year of age, he developed generalized convulsions, and evaluation in an emergency room revealed a plasma creatinine concentration of 6 mg/dl. An abdominal ultrasound examination revealed marked bilateral hydronephrosis with cortical thinning, and a thickened, trabeculated bladder. Following bladder catheterization and fulguration of the PUV, the plasma creatinine concentration dropped to 0.8 mg/dl, and the patient's symptoms resolved. He did well for the next 12 years, with normal growth velocity and normal psychosocial development. During this time, his plasma creatinine concentration remained less than 1 mg/dl, and he did not have interval renal ultrasonography. At 14 years of age, he developed acute pyelonephritis, and plasma creatinine increased to 3 mg/dl. Despite antibiotic treatment, renal function continued to deteriorate, and he required dialysis and renal transplantation before he graduated from high school.

This case demonstrates the variable 'silent phase' of congenital obstructive uropathy. It is likely that the patient had a significant reduction in nephron number, and had progressive tubulointerstitial disease. The lack of a normal urinary tract and marginal renal function contributed to his renal decompensation with acute pyelonephritis. It is very likely, however, that even without the acute infection, he would have had progressive deterioration over time.

The future

How can we develop better means of diagnosing obstructive uropathy, selecting patients for surgical intervention, and preventing the progression of renal insufficiency? The first step will be to define the natural history of obstructive uropathy to generate measures of injury and functional impairment (Table 33.3).[80] This will also require a better knowledge of the

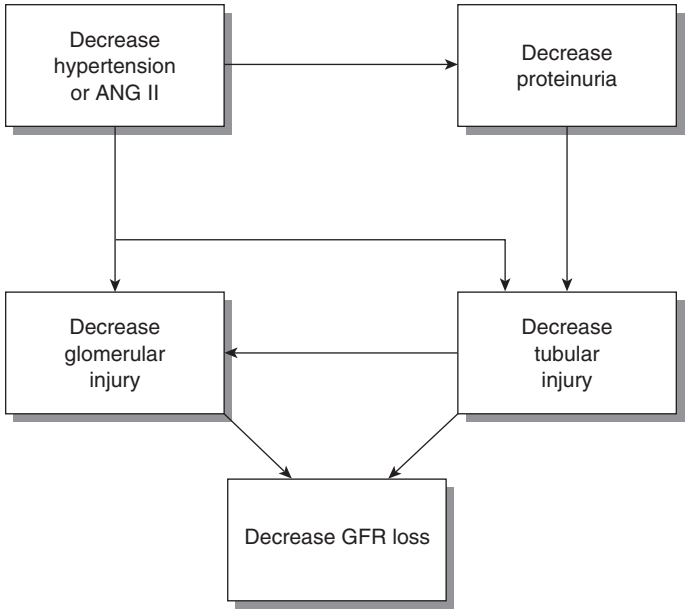

Figure 33.12 The interactions of hypertension and proteinuria on glomerular and tubular injury in progressive renal disease. ANG II, angiotensin II; GFR, glomerular filtration rate. (Reproduced with permission from Hebert et al.[75])

Table 33.2 Inhibition of angiotensin: therapeutic use in congenital obstructive uropathy

Advantages
Controls hypertension
Reduces proteinuria
Attenuates fibrosis
Disadvantages
Impairs renal development
Reduces GFR
Exacerbates sodium wasting

GFR, glomerular filtration rate.

Table 33.3 Research needs in congenital obstructive uropathy

- Define the natural history of obstructive nephropathy by developing biomarkers in humans and in animal models to generate measures of injury and functional impairment
- Elucidate the cellular and molecular basis of renal maldevelopment, focusing on the link between functional and developmental pathophysiology
- Develop a clinical research infrastructure with the creation of comprehensive registries of patients to include urine, plasma, and tissue samples, as well as standardized imaging. This should lead to clinical trials

Table reproduced with permission from Chevalier and Peters.[80]

Table 33.4 Potential biomarkers of congenital obstructive uropathy

Gross anatomy: ultrasound, MRI
Renal function: nuclide scan, markers of tubular function
Microscopic anatomy: biopsy/histology
Cellular function: gene and protein expression in tissue and excretion in urine

MRI, magnetic resonance imaging.
Table reproduced with permission from Chevalier.[81]

cellular and molecular basis of renal morphogenesis, and of the link between altered structure and function. Ultimately, the goal should be to develop repositories of tissue, blood, and urine samples, and to develop standardized imaging so that large multicenter clinical trials can be established (see Table 33.3).[80]

A key factor in addressing these factors will be the development of surrogate end points, or biomarkers.[81] Such parameters have been developed to characterize acute renal failure, renal transplant rejection, and polycystic kidney disease (all tubular disorders). The identification of biomarkers for congenital obstructive uropathy will require advances in all of the points listed in Table 33.3. To date, imaging by renal sonography has been limited by the operator-dependency of the technique as well as by the resolution. The evaluation of renal function and the dynamics of the obstruction by diuretic nuclide scan are useful but poorly standardized (Table 33.4). Magnetic resonance imaging (MRI) offers promise by combining anatomic and functional information with higher resolution (Figure 33.13).[82] As discussed above, the predictive value of fetal urine chemistries (such as sodium or β_2-microglobulin) is not generally satisfactory.

While histologic analysis of renal tissue from infants or children with obstructive uropathy correlates poorly with renal function,[83] molecular markers are likely to improve the value of biopsy (see Table 33.4). As shown in Figure 33.6, TGF-β_1 plays a central role in the pathophysiology of obstructive uropathy, and the expression of this cytokine is increased in dysplastic tubules.[84] Laser capture microscopy may provide an additional powerful tool to isolate changes in the expression of specific markers by discrete renal compartments or components of the nephron. Urinary excretion of TGF-β_1 may also identify patients with significant urinary tract obstruction, even if it is unilateral (Figure 33.14).[85] Additional candidate biomarkers in the urine include monocyte chemoattractant protein-1 (MCP-1), which is increased in patients with UPJ obstruction, and epidermal growth factor, which is decreased in UPJ obstruction.[86] Finally, DNA microarray and proteomics may reveal new candidate biomarkers that have yet to be considered.[29]

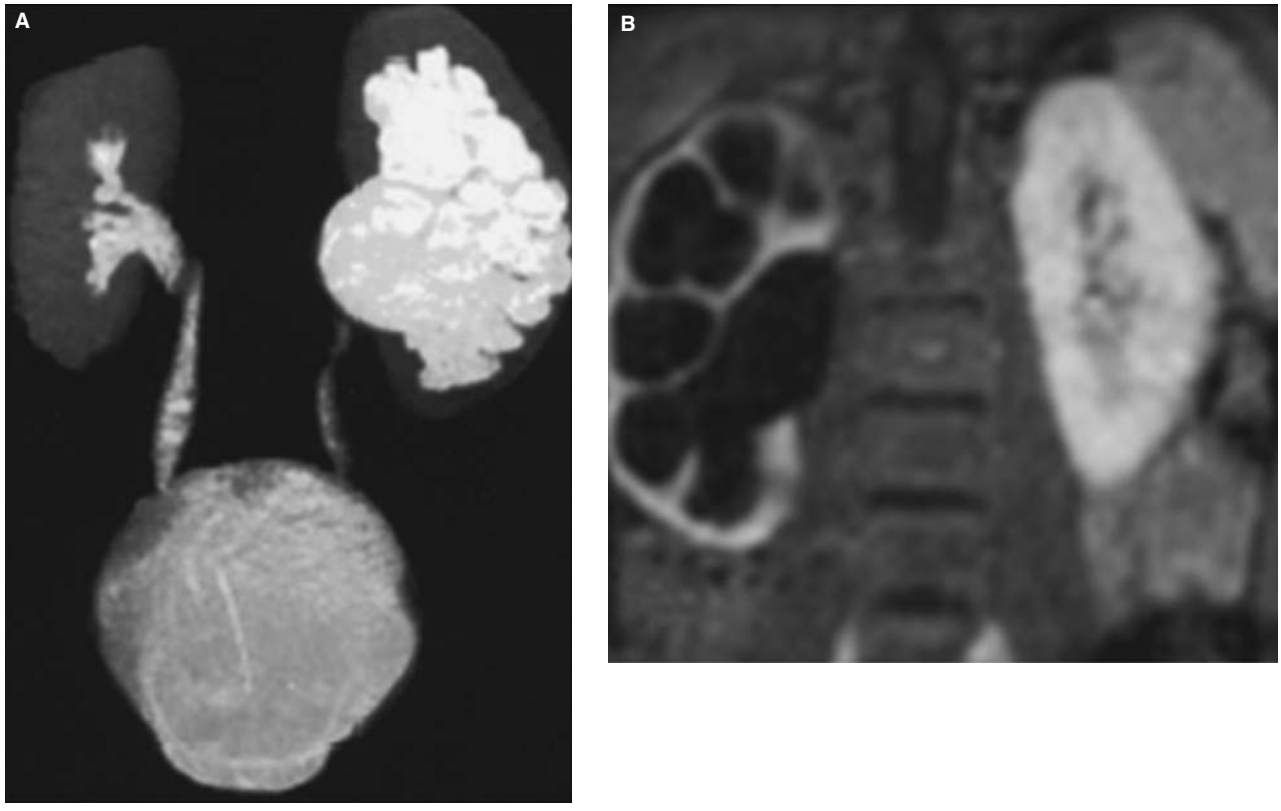

Figure 33.13 (A) Magnetic resonance imaging (MRI): maximum intensity projection reconstruction after Gd-DTPA infusion in a patient with left ureteropelvic junction (UPJ) obstruction. (B) Differential function determination in post-Gd-DTPA MRI in UPJ obstruction (R:L ratio 28:72). (Reproduced with permission from Perez-Brayfield et al.[82])

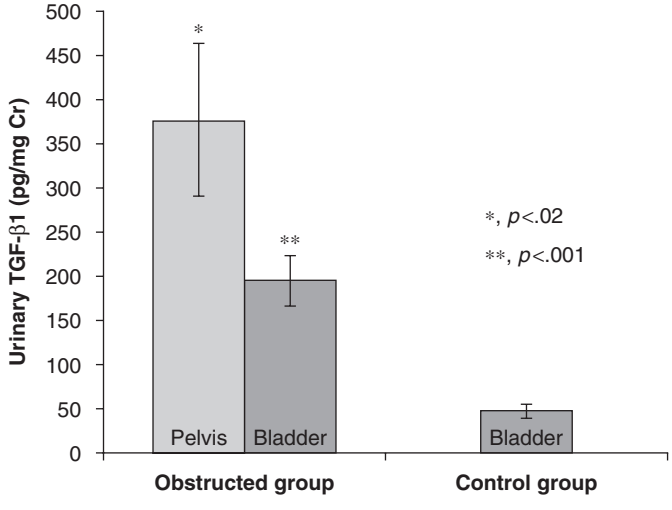

Figure 33.14 Mean urinary transforming growth factor-β_1 (TGF-β_1) concentration in children with upper tract urinary obstruction vs controls, as corrected for creatinine (Cr). Bladder urine TGF-β_1 in obstructed group was fourfold that in the control group. In the obstructed group, mean renal pelvic urine TGF-β_1 was two-fold that in bladder urine. Bars represent mean ± SEM. (Reproduced with permission from Furness et al.[85])

Advances in the medical management of congenital obstructive uropathy may involve interventions at a variety of the pathways shown in Figure 33.6. Experimental studies in neonatal mice with UUO have shown that reduction in the expression of endogenous selectins (adhesion molecules) can reduce interstitial macrophage infiltration and tubular apoptosis.[31,87] A reduction in the number of copies of angiotensinogen results in a proportional decrease in interstitial fibrosis in the obstructed kidney of the neonatal mouse.[88] Treatment with growth factors such as epidermal growth factor or insulin-like growth factor-1 (IGF-1) can dramatically reduce apoptosis, tubular atrophy, and renal interstitial fibrosis in neonatal rats with UUO.[89,90] Progress in novel therapeutics for obstructive uropathy will require additional studies of appropriate animal models and, eventually, clinical trials.

Concluding remarks

Congenital obstructive uropathy constitutes a major cause of renal insufficiency and renal dysfunction in infants and children. The cellular and molecular basis for renal maldevelopment

remains poorly understood, and many questions remain regarding the optimal diagnostic approach and treatment of these patients. Close partnership between pediatric nephrologist and pediatric urologist is essential to integrating medical and surgical management, as well as transition to appropriate specialists when the patient reaches adulthood.

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34 Voiding disorders

Hans G Pohl and C Gerry Henderson

Derangements in the normal pattern of micturition result in a variety of urinary tract symptoms and morbidity. Such voiding disorders range from mild manifestations that represent no more than a social nuisance, to severe dysfunctional elimination associated with recurrent cystitis and/or acute pyelonephritis (APN), hydronephrosis, and vesicoureteral reflux (VUR). Voiding disorders in children result from immature bladder function, abnormal voiding habits, and urinary sphincter dysfunction. Recurrent urinary tract infections (UTIs) and upper urinary tract changes due to voiding dysfunction are generally seen in severe sphincter dysfunction associated with high bladder pressure generated during voiding, incomplete bladder emptying, and/or functional bladder outlet obstruction. Rarely, anatomic causes of incontinence are encountered from conditions such as spina bifida, posterior urethral valve, and prune-belly syndrome that can affect the bladder and/or the urinary sphincter. Diet and social factors also influence toileting behavior and need to be addressed early in the management of these patients.

Normal voiding

A normal voiding cycle is a two-phased process, consisting of low-pressure and adequate volume bladder filling, followed by complete evacuation of the bladder.[1] Both of these phases of the voiding cycle are coordinated and active processes. Bladder filling requires inhibition of bladder contraction and increased tone of the urinary sphincter complex. As the bladder approaches fullness, tension receptors in the bladder wall trigger afferent nerves that send signals of the need to void. Voluntary voiding involves inhibition of sphincter contractions and coordinated contraction of the bladder smooth muscle.

Bladder filling in neonates is followed by reflexive emptying (voiding reflex). This reflexive micturition cycle is controlled by the sacral spinal cord, and occurs approximately hourly. After 6 months of age, the urinary volumes increase and the frequency of voiding decreases as the control of voiding shifts from the sacral cord to the pontine voiding center, thus establishing the spinobulbospinal reflex pathway.[2,3]

Around the age of 2, the child develops conscious sensation of bladder fullness and has urge incontinence. Between 2 and 4 years of age, the child acquires voluntary control of bowel and bladder function according to the following sequence:

1. nocturnal bowel control
2. daytime bowel control
3. daytime bladder control
4. nocturnal bladder control.

Thus by 4 years of age, the majority of children demonstrate an adult voiding pattern. The timing of this sequence is influenced by ethnic, cultural, economic, and individual family differences. In the United States, the mean age at which daytime urinary control is achieved is 2–3 years of age, but may vary from 1 to 5 years.[4] Five to 10 percent of children aged 4–9 years may experience at least some daytime wetting.[4] In general, most school-aged children void between 4 and 6 times daily.[4]

Since many functional and anatomic disturbances of voiding manifest as wetting, we have organized the discussion of these entities by the likelihood of renal damage associated with each condition (Table 34.1). Thus, conditions such as daytime frequency syndrome, giggle incontinence, and overactive bladder are not associated with upper tract injury and so do not require extensive imaging or intensive follow-up. Alternatively, voiding disorders, such as dysfunctional elimination, Hinman syndrome, posterior urethral valve, and neurospinal dysraphisms, may be the cause of upper urinary tract deterioration by virtue of high-pressure voiding and urinary tract infection. Three miscellaneous conditions, cerebral palsy, attention deficit hyperactivity disorder and hypercalciuria, are addressed as well.

Epidemiology

Urinary incontinence is frustrating for parents, socially ostracizing to patients, and is often regarded as a clinical nuisance by many physicians. It is estimated that approximately 417 000 visits are made to pediatrician's offices annually for incontinence of all etiologies, with primary nocturnal enuresis (PNE) representing 38% of these cases. Seventy-five percent of such children are evaluated between 3 and 10 years of age, and 15–20% are between 11 and 17 years of age.[5]

The rate of outpatient visits for PNE in both commercially insured and Medicaid populations has more than doubled from approximately 100 per 100 000 children to 283 per 100 000 children in the 6-year period from 1994 to 2000.[5] Whether there is a

Table 34.1 Clinical categorization of voiding disorders

Low risk for upper tract deterioration
Daytime frequency syndrome
Postvoid dribbling
Giggle incontinence
Stress urinary incontinence
Primary nocturnal enuresis
Paradoxical incontinence or ectopic ureter in girls
Sensory deficient bladder
Overactive bladder
High risk for upper tract deterioration
Dysfunctional elimination
Non-neurogenic, neuropathic bladder or Hinman syndrome
Posterior urethral valve
Neurospinal dysraphism
Miscellaneous causes
Cerebral palsy
Attention deficit hyperactivity disorder
Hypercalciuria

true increase in the prevalence of childhood incontinence, or merely an increased awareness of the need to treat has led to increased referrals is unclear. Urinary incontinence in children must be evaluated in the context of the child's age, since attainment of daytime and nighttime urinary control follows a predictable maturational process. For instance, urinary incontinence is quite a normal phenomenon in children under the age of 3 years.

Diseases with low risk for upper tract deterioration

Daytime frequency syndrome

Daytime frequency syndrome (DFS) consists of acute-onset urinary urgency and frequency with or without rare episodes of incontinence and without any definable clinical cause. DFS primarily affects boys 4–8 years of age (mean, 4.5 years), and is more prevalent in the spring and fall. No certain etiology for the syndrome has been established, although some authors postulate that DFS is caused by psychosocial stress with seasonal variation.[6–10] DFS is characterized by urinary frequency without dysuria, which occurs every 10–20 minutes during the daytime, but abates completely during sleep. Nocturnal enuresis is not a feature of DFS. Evaluation of the patient is by history and physical examination, with a normal urinalysis and a negative urine culture. DFS is a self-limiting disorder and requires support and reassurance. Resolution requires from 2 days to 16 months, with an average of 2.5 months.[7,11]

Postvoid dribbling

Postvoid dribbling, or vaginal voiding, occurs in prepubertal girls who are thin or obese. In both cases an abnormal position precludes the girl from adequately opening her legs, thus causing vaginal trapping of urine. Once voiding concludes, the pooled urine drains shortly after assuming an upright posture. The diagnosis may be based on history alone, with dribbling occurring shortly after voiding. Occasionally, perineal itching suggests yeast infection. The itching is caused by chemical irritation and does not need to be treated with antifungals.

The physical examination is usually normal, or may reveal labial adherence or labiovulvar erythema. Radiographic evaluation is not warranted. Treatment consists of having the girl sit on the toilet facing the wall (backwards), with her legs spread apart. If she is unable or unwilling to do this, a stool or seat adaptor can be used, although these are usually cumbersome. If labial adherence is present, precisely applied topical estrogen (Premarin ointment, 0.625 mg) applied twice daily for no longer than 6 weeks is usually curative. Rarely, does labial adherence require surgical lysis.

In males, urethral pooling, usually in a congenital or acquired urethral diverticulum, may cause postvoid dribbling. The physical examination is either normal or may show ventral penile swelling, especially following voiding. In most circumstances, the boy has previously undergone a hypospadias repair. The treatment is surgical.

Giggle incontinence

Giggle incontinence, or enuresis risoria, is a disorder characterized by complete bladder emptying with giggling, laughter, or exertion. This condition may be related to cataplexy, a part of narcoleptic syndrome complex. Genetically, giggle incontinence has been linked to human leukocyte antigen (HLA) DR2 and has a strong familial predisposition.[12,13] The condition occurs primarily in peripubertal girls, is rarely seen in boys, and can persist into adulthood.[13,14] The patient is dry during day and night but experiences daytime bladder emptying associated with giggling or laughing.

Characteristic history alone is sufficient for making the diagnosis of giggle incontinence. Physical examination and urinalysis are normal in such cases. Urodynamic and radiographic evaluation is not warranted. Frequent voiding, especially prior to social engagements, can be adequate treatment. Anticholinergics or Kegel exercises are usually not helpful; however, methylphenidate has been shown to decrease the frequency of the episodes, with as-needed or continuous usage.[13,15] Conditioning therapy with low-voltage electric shocks to the back of the hand has also been shown to be effective.[16]

Stress urinary incontinence

Stress urinary incontinence is the loss of urine with physical activity, coughing, or sneezing. This occurs most commonly in adolescent and young, adult female athletes. Nygaard and associates studied 156 nulliparous college varsity athletes with a mean age of 19.9 years.[17] The prevalence of incontinence while

participating in their sports was 28%. Forty percent of the females had noted incontinence in high school and 17% in junior high school.[17,18]

The diagnosis of stress incontinence is made by history. Physical examination and urinalysis are usually normal. Radiographic examination is not warranted, unless evidence of spina bifida occulta exists on physical examination (e.g. hair tuft, lipoma, asymmetric gluteal crease). In these cases a magnetic resonance imaging (MRI) scan of the spine should be obtained to exclude spinal cord tethering.

Primary nocturnal enuresis

Primary nocturnal enuresis (PNE) is bedwetting in an individual who has never been dry at night. When the child begins wetting the bed after a period of nighttime continence has been achieved, enuresis is termed *secondary*.[19] PNE is usually *monosymptomatic* and is not associated with daytime symptoms. While PNE is considered normal in infants, society expects night dryness by 5 years of age. PNE affects about 15% of 5-year-old children but prevalence diminishes gradually to only 3% in adolescents.[20,21] A familial form of the disease, characterized by an increased incidence of PNE in children of enuretic parents, is well known.[22]

The pathogenesis of PNE is unclear, but dysfunction of bladder, kidneys, and central nervous system has been implicated. Urodynamic evaluation of enuretic children during waking and sleep has shown that many children with PNE have reduced bladder capacity and demonstrate overactivity, like the infantile bladder.[19] One criticism of these studies has been the possible inclusion of children with daytime symptoms. One study demonstrated that the incidence of bladder overactivity might only be 16% in pure monosymptomatic enuretics.[19] Nevertheless, it appears that children with enuresis may be a heterogeneous group, with some displaying reduced functional bladder capacity only during sleep. Other children with monosymptomatic enuresis have bladder overactivity during day and night. These patients manage to compensate during wakeful states and do not have daytime wetting. At least one study has challenged the dictum that enuresis is characterized by complete evacuation of the bladder by demonstrating elevated postvoid residual urine measurements (>10% of bladder volume) and abnormal bursts of electromyography activity suggesting sphincter dyssynergia.[23]

Urine production usually decreases at night under control of the circadian rhythm of secretion of antidiuretic hormone (ADH).[24] Loss of the normal nighttime production of ADH results in polyuria that can exceed the functional capacity of the bladder and result in enuresis. Much of the work on ADH mediation of enuresis has been done by the Aarhus and colleagues.[25] They demonstrated that nocturnal urine production was significantly greater than daytime urine production in some enuretic children.[25] This finding was explained when significantly lower nocturnal levels of ADH were found in concert with large volumes of dilute urine in enuretic children.[26] Recently, aquaporin channels, ADH-responsive transmembrane proteins responsible for urinary concentration, have been implicated in the pathophysiology of enuresis.[27]

A maturational delay in the ability to sense bladder filling and to inhibit the bladder contraction until wakefulness has been implicated as a causative factor in enuresis.[28,29] There are mixed reports about a sleep arousal and developmental delay in enuresis. Some authors claim that enuretics are more difficult to arouse. However, the siblings of such patients have been found to be equally as hard to awaken.[30–33]

Treatment of nocturnal enuresis is divided into three categories: observation, behavioral, and pharmacologic. Observation is sufficient if the wetting is not a major social or family disruption, since PNE has an annual spontaneous resolution rate of 15%. Behavioral modification, or conditioning therapy in the form of an enuretic alarm, requires significant motivation of the parents and child and up to 6 months of use. This is, however, the most effective form of treatment available, with permanent cures occurring in over 90% in motivated families. The relapse rate can be 25–30% after only 6–8 weeks of using the alarm device.[34,35] Pharmacotherapy for PNE is discussed in detail below.

Paradoxical incontinence

Paradoxical incontinence (PI) is the term applied to continuous dribbling, despite a normal voiding pattern. This phenomenon is exclusively seen in girls, and is caused by an ectopic ureteral insertion distal to the external urinary sphincter complex. The most common ectopic ureteral sites are the urethra (35%), vaginal vestibule (34%), and vagina (25%).[36] Although boys may also have distally inserting ectopic ureters, the insertion site (e.g. seminal vesicals, vas deferens) is always proximal to the external urinary sphincter, and thus, incontinence is prevented.[37,38]

The physical examination should include inspecting the girl's perineum in the frog-legged position with the labia spread. With patience, urine can often be seen pooling in the vaginal vestibule. Radiologic investigation typically relies on identifying the ectopic ureter, or the renal unit it subtends. Renal–bladder ultrasound (RBUS), voiding cystourethrogram (VCUG), intravenous pyelogram, and computed axial tomography have been used to identify the renal unit responsible for the incontinence. However, the renal unit attached to such an ectopic ureter is invariably dysplastic, and often poorly visualized by traditional imaging. Pattaras and colleagues reported on a small cohort of girls with PI from ectopic ureters.[39] Nuclear renal scintigraphy with Tc 99 m dimercaptosuccinic acid (DMSA) reliably detected and localized the hypoplastic ectopic kidneys and poorly functioning upper pole moieties in each case. Thus, once the clinical presentation suggests PI from an ectopic ureter, nuclear renal scintigraphy should be considered during the initial radiologic evaluation.[39–41]

Sensory deficient bladder

Young girls, and occasionally boys, will avoid urinating for an extended period of time. Typically, the patient will awaken, eat,

and go to school without voiding. The first void will often be at midday or even after school. The patients often rush to the toilet and may wet themselves on the way to the toilet or be damp already. The clinician makes the diagnosis by asking the following three questions:

- Does the patient urinate on awakening in the morning?
- Does she/he use the toilet at school?
- How many times does she void during a typical day?

The patient's symptoms consist of dysuria, urgency with a full bladder, bedwetting, and/or urinary dribbling. The patient may present with a UTI or for work-up of a fever and abdominal pain. Physical examination may be normal or demonstrate a palpable bladder. Urinalysis is likely to show bacteriuria, and urine culture may be positive. A pre- and postvoid renal bladder ultrasound should be done to evaluate postvoid residual urine. The infection should be treated and antibiotic prophylaxis continued if there have been multiple UTIs and until effective frequent bladder emptying is achieved.

Overactive bladder

Overactive bladder (OAB) with its many synonyms (bladder instability, urge syndrome, hyperactive bladder, persistent infantile bladder, detrusor hypertonia) is the most common voiding dysfunction of childhood. Its occurrence peaks between 5 and 7 years of age; it has an incidence of 57.4%, with a female preponderance (60.1% in females and 38.9% in males).[42] The etiology of this disorder is thought to be delayed functional development of cortical inhibitory control over the voiding reflex mediated through the reticulospinal pathways or in the inhibition center of the cerebral cortex.[43–46] In response to the urge to urinate, the child learns to contract the external urinary sphincter in order to suppress the bladder contraction and delay voiding. In some circumstances, the child can be seen running to the toilet in response to the urgency, and, occasionally, when the toilet is not reached in time, incontinence occurs. Other sufferers are able to remain dry if they concentrate on their bladders, but are often wet at play or when absorbed in an activity of interest to them. Holding maneuvers (leg crossing, squatting, Vincent's curtsey) are a common observation by parents and are the child's attempt to suppress the bladder contraction by exerting pressure on the external urinary sphincter.[47]

Sphincter tightening and holding maneuvers result in increased bladder muscle stretch, since contraction occurs against a fixed resistance. The OAB is associated with vesicoureteral reflux in 20–50% of children. In such circumstances, management of VUR should include addressing the OAB as a clinical issue. Otherwise, spontaneous resolution of the VUR may be impeded, and recurrent UTIs may occur.[48–51]

Although imaging is not warranted in the majority of children with OAB, those who are resistant to conservative management may benefit from pre- and postvoid renal bladder ultrasound with an assessment of postvoid residual urine volume. The sonogram can provide information regarding upper urinary tract dilatation, bladder wall thickening, and the child's ability to empty the bladder. Voiding cystourethrography and urodynamics are only recommended if febrile UTIs have been present, or evidence of urinary tract decompensation has been documented sonographically.[52,53] Frequently, urodynamic findings include reduced functional bladder capacity with uninhibited bladder contractions.[46]

Conservative management of the OAB consists of timed voiding, anticholinergic therapy, prophylactic antibiotics, and treatment of any underlying constipation.[51,52,54–59] The success of timed voiding depends on the child's motivation to urinate before a spontaneous bladder contraction. If this schedule would require the child to void at a socially unacceptable frequency, anticholinergic medication should be considered. When used appropriately, anticholinergic medications offer a reasonable degree of success. These measures, in combination with elimination of caffeine, result in resolution of symptoms in 87% of children treated conservatively.[52] The child's parents must understand that treatment is a long-term process, taking an average of 2.7 years, with a range from 0.2 to 6.6 years. Since urinary infection may promote bladder instability, any active UTI should be treated with appropriate antibiotics. The patient should then be placed on prophylaxis with trimethoprim–sulfamethoxazole or nitrofurantoin until a normal voiding pattern has been established.

Diseases at high risk for upper tract deterioration

Dysfunctional elimination

Dysfunctional elimination syndrome (DES) encompasses constipation, urge incontinence, voiding postponement, infrequent voiding, and urinary retention, which develop from a learned response to bladder overactivity.[50,60,61] In an effort to avoid incontinence, the patient contracts the sphincter complex and/or postures, which effectively suppresses the urinary or fecal urgency temporarily.

In its mildest form, DES is characterized by infrequent bowel movements, hard stools requiring straining, voiding postponement, and a strong or 'staccato' stream that results in daytime urinary and/or fecal incontinence. More severe forms of DES may present with incontinence, UTIs, bladder wall changes (distention, thickening, trabeculations, or reduced bladder contractility), VUR, and hydronephrosis.[45,51,62–64]

There is a close relationship between VUR and dysfunctional elimination. VUR can be identified in 30–50% of patients with DES.[51,55,59,65] However, this association may be biased, since the majority of patients included in the studies presented with recurrent UTIs, a group known to have a high prevalence of VUR (30–35%). Koff et al found that among 143 patients felt to have primary VUR, 43% were identified as having significant bowel and bladder disturbances.[51] In the children with VUR and dysfunctional elimination, breakthrough UTIs

occurred in 82%, whereas only 18% of children with VUR and no evidence of dysfunctional elimination had breakthrough UTIs.[50] These data demonstrate the influence which dysfunctional elimination has on the pathogenesis of UTI and underscores the notion that VUR itself is not a risk factor for UTI. Several studies have reported improved resolution rates of VUR in children who were also provided therapy for coexisting dysfunctional elimination, in addition to standard antimicrobial prophylaxis. Conversely, failure to address dysfunctional elimination results in a higher failure rate following antireflux procedures.[50,51,55,59] Although many children with VUR do not have abnormal voiding patterns on urodynamic investigation, and most children with DES do not have VUR, it is recommended that children with recurrent UTIs and VUR be screened for dysfunctional elimination as part of the initial evaluation.

DES is clinically suspected from the presenting history of the patient. The physical examination is usually normal, but may also reveal a palpable bladder and possibly palpable stool in the colon. An abdominal radiograph may demonstrate fecal retention. RBUS should be used to screen for increased postvoid residual urine volumes. A VCUG is not warranted unless documented febrile UTIs have occurred and one suspects VUR.[53]

Treatment should first address the bowel dysfunction, using cleansing with oral laxatives and enemas if needed. A maintenance program should involve increasing the daily dietary fiber intake as well as by supplementation, with a goal of a daily bowel movement. Behavioral modification should also focus on retraining urinary elimination to ensure regular and complete evacuation of the bladder. Children with bladder instability can be treated with anticholinergics such as oxybutynin, hyoscyamine, or tolterodine, with the caveat that treatment of constipation must be addressed concurrently.

Non-neurogenic neurogenic bladder (Hinman syndrome)

Non-neurogenic neurogenic bladder represents extreme voiding dysfunction involving the lower urinary tract and affecting the upper tracts in the absence of any neurologic dysfunction.[62,66] Hinman syndrome represents functional bladder outlet obstruction from learned discoordination between bladder contraction and sphincter relaxation. The majority of patients are young males who have day and night wetting associated with chronic urinary retention, fecal retention and soiling, recurrent UTIs, and impaired renal function.[62] In addition to the clinical presentation, one may also elicit a social history significant for divorced, domineering parents, parental alcoholism, and drug, sex, or generalized abuse. Physical examination, as in DES, may only demonstrate fecal or urinary retention, and the neurologic examination is entirely normal. The diagnosis is often suggested when evidence of hydronephrosis is seen on a sonogram obtained during the evaluation for suspected DES. Some patients may present with manifestations of advanced renal dysfunction and complications from it. Voiding cystourethrography often shows a dilated, trabeculated bladder with VUR. An MRI scan should be obtained to exclude spina bifida occulta. These boys should be referred for urodynamic studies. Since many boys ultimately require intensive bladder retraining with biofeedback, it is practical to place a suprapubic cystostomy tube under anesthesia through which urodynamic studies and multiple biofeedback sessions can be performed without the need for repeated catheterizations. Botulinum toxin injection of the external sphincter has been performed successfully when biofeedback has failed.[67,68]

Posterior urethral valves

Three variations of congenital urethral membranes (valves) are generally referred to in the literature. Of these, only two are truly associated with urinary obstruction and are of clinical relevance. A type I valve, which represents anomalous insertion of the mesonephric duct into the fetus' cloaca, is found cystoscopically between the prostatic urethra and external urinary sphincter and accounts for 95% of clinical cases.[69] The less common (5%) type III valve represents incomplete dissolution of the urogenital membrane and is encountered within the membranous urethra beyond the external sphincter.[70] Currently, most cases of PUV are diagnosed antenatally by ultrasonography. The characteristic imaging findings in such fetuses consist of bilateral severe hydronephrosis, bladder distention and/or bladder wall thickening, perinephric urinoma or ascites, and amniotic fluid abnormalities are seen in a male fetus.[71]

Despite endoscopic ablation of the valve in the newborn period, up to 50% of these boys will have incontinence well past toilet training, possibly because of associated primary bladder dysfunction.[72] Urodynamic assessment has shown changing patterns of bladder dysfunction, with overactivity predominating in childhood, leading to myogenic failure in adolescence.[73] Unfortunately, bladder dysfunction appears to correlate with deterioration in renal function through as-yet uncertain mechanisms.[72] Ultimately, most boys can achieve continence through institution of clean intermittent catheterization and/or anticholinergic medication, or surgical reconstruction of the urinary tract. Urodynamic studies should be performed to guide therapy, with the goal of ensuring low-pressure bladder filling and complete and regular evacuation of urine.

Neurospinal dysraphisms

Myelomeningocele accounts for 90% of all spinal dysraphic states, and it affects the lumbar, sacral, thoracic, and cervical spine, in decreasing prevalence.[74] An effective physical examination in patients with myelodysplasia would include palpation of the abdomen for bladder distention and fecal retention. In addition, urinary sphincter tone can be estimated, based on inspection of the anal sphincter for laxity and reflexive contraction. Since the level of the lesion does not predict the type or degree of lower urinary tract dysfunction, a neurologic and urodynamic examination of these patients is crucial.

Urodynamic studies immediately following newborn closure of the spinal defect and later have shown three main categories of prevalent bladder function:

- a coordinated bladder and sphincter (19%)
- discoordination with or without bladder overactivity (45%)
- complete paralysis (36%).[75–77]

These patterns are not fixed and can change over time, resulting in varying patterns of bladder dysfunction.

RBUS may show a dilated bladder with bladder wall thickening and dilated upper urinary tracts. VCUG reveals a trabeculated bladder and VUR may be present. MRI is the test of choice for anatomic detail of the spinal cord.[78] It is used to evaluate tethering of the spinal cord, syrynx, or hydromyelia, increased intracranial pressure due to ventriculoperitoneal shunt malfunction, and partial herniation of the brainstem and cerebellum. Radiologic evaluation is repeated any time there is a change in neurologic, orthopedic, or urodynamic assessment.

Treatments are aimed at preserving nephron function and facilitating low-pressure voiding. Clean intermittent catheterization alone, or in combination with anticholinergics, is used to keep the intravesical pressure $< 40\ cmH_2O$.[79–81] Rarely, a vesicostomy must be performed when the above therapies are not sufficient in adequately decompressing the bladder.[82,83]

Miscellaneous causes

Cerebral palsy

Cerebral palsy (CP), a non-progessive perinatal brain injury caused by infection or hypoxia, is characteterized by neuromuscular disability, specific symptoms complex, or cerebral dysfunction. Its incidence – currently 1.5 per 1000 live births – is increasing as smaller, younger premature infants are surviving.[84] Incontinence in children with CP is related to the degree to which the physical disability impairs reaching the toilet in time. Continence often develops at a later than expected age. If dryness is not achieved by late childhood or early puberty in a child who is physically capable and who appears trainable, further evaluation by urodynamic testing is recommended.[85] The most common clinically relevant urologic findings are exaggerated sacral reflexes, detrusor overactivity, and/or detrusor-sphincter dyssynergia.[86] Radiographic evaluation is not generally necessary.[87] Anticholinergics are able to provide relief of uninhibited bladder contractions in most patients with these complaints. If the child has large volumes of postvoid residual urine, clean intermittent catheterization should be advocated.

Attention deficit hyperactivity disorder

Children with attention deficit hyperactivity disorder (ADHD) have a greater risk of daytime (ninefold) and nighttime (three-fold) enuresis than age-matched controls.[88] The risk of daytime enuresis appears to increase with age, whereas the risk of nighttime enuresis lessens, as children get older.[88] Some improvement in wetting may be seen following the use of methylphenidate.

Hypercalciuria

Idiopathic hypercalciuria has been identified in 20–30% of children with hematuria, dysuria, frequency-urgency syndrome, or voiding dysfunction.[89–91] It is postulated that the high concentrations of calcium in the urine irritate the bladder, causing involuntary incontinence. Although most nephrologists accept the definition of hypercalciuria as urinary calcium excretion > 4 mg/kg/day in children with urolithiasis, some have recommended that urinary calcium excretion of > 2 mg/kg/day be considered as the threshold for defining hypercalciuria in children with enuresis or dysuria.[90,92] Successful treatment of the hypercalciuria can result in reduction of urinary symptoms and wetting in these patients.[92,93] Treatment is based on dietary measures aimed at decreased salt and oxalate intake and increased dietary fluid intake. Dietary calcium intake is generally not curtailed, since it is important in maintaining proper bone health in a developing child. Thiazide diuretics are helpful in reducing hypercalciuria when dietary measures fail.

Evaluation

History

The diagnosis of childhood voiding disorders is made primarily by history and physical examination. Radiologic, laboratory, and complex urodynamic evaluation are rarely required but may be considered in circumstances when the clinical manifestations include UTI (febrile and afebrile), when physical examination suggests neurologic dysfunction, or when simple behavioral or pharmacotherapy has been unsuccessful.

Elimination diary

Obtaining an accurate history of incontinence is of paramount importance, and may be sufficient to arrive at a diagnosis. An assessment of the onset, pattern, severity, and circumstances surrounding the incontinence episodes should be noted. The interview should also include the child, depending on the child's age and maturity level.

We have found it useful to provide families with a questionnaire in advance of the initial evaluation, such that observations can be made prior to arriving at the clinic (Figure 34.1). These surveys document the degree to which wetting occurs during the day and night, the pattern of urinary and fecal elimination, specific behavioral patterns which can be observed in conjunction with wetting, drinking habits, and whether a UTI has coexisted with the wetting disturbance. Additionally, parents are requested to record the number of times the child voids or exhibits wetting during a 2-day interval (Figure 34.2). Armed with this preliminary information, one can then obtain a more detailed history that focuses on pertinent positive observations.

Last Name ☐ **ID #** ☐

First Name ☐

Date of Visit

Date of Birth

1. Is your child toilet (potty) trained? O Yes O No
2. At what age was he/she toilet trained? ☐ Years

Questions about your child's wetting.

3. Does your child wet himself/herself during the day? O Yes O No
4. If yes, how often might your child wet himself/herself?
   ☐ Once a day ☐ Every other day ☐ Once a week ☐ Not sure
   ☐ Two or more times a day ☐ Twice a week ☐ Once every two weeks
5. Does your child wet the bed at night? O Yes O No
6. If yes, how often does your child wet the bed at night?
   ☐ Every night ☐ Twice a week ☐ Once every two weeks
   ☐ Every other night ☐ Once a week

Questions about your child's urinating habits.

7. Does he/she need to be reminded to urinate? O Yes O No
8. Does your child urinate soon after waking-up? O Yes O No
9. Does he/she urinate at school? O Yes O No
10. Does your child urinate after coming home from school? O Yes O No
11. Does your child urinate just before bedtime? O Yes O No
12. Does your child squat, cross his/her leg, squirm or wiggle before a leak? O Yes O No
13. When your child wets does he/she have no idea that it happened? O Yes O No

Questions about your child's drink habits.

14. Does your child drink with meals? O Yes O No
15. What does your child drink?
    ☐ Water ☐ Caffeinated (Coke, Pepsi, Chocolate, Coffee)
    ☐ Milk
    ☐ Juice
16. How many cups of fluid does your child drink each day?
    ☐ 1–3 cups ☐ 4–6 cups ☐ 7–10 cups ☐ Not sure

Figure 34.1A Voiding questionnaire part A.

Last Name _____ **First Name** _____

Questions about your child's bowel movements.

17. Is your child's underpants stained with feces? O Yes O No
18. If yes, how often might this happen?
    - ☐ Once a day
    - ☐ Every other day
    - ☐ Once a week
    - ☐ Not sure
    - ☐ Two or more times a day
    - ☐ Twice a week
    - ☐ Once every two weeks
19. How often does your child usually have a bowel movement?
    - ☐ Once a day
    - ☐ Every other day
    - ☐ Every 3 days
    - ☐ Every 4 or more days
    - ☐ Not sure
20. Does your child need reminding to have a BM? O Yes O No

Questions about your child's urinary tract infections.

21. Has your child had a urinary infection treated in the last 12 months? O Yes O No
22. How was the specimen collected?
    - ☐ Bag
    - ☐ Clean Void, Midstream
    - ☐ Catheter
    - ☐ Not sure
23. How many infections has your child been treated for in the last 12 months? _____ Times
24. Which symptoms did he/she have with the infection?

Wetting?	O Yes	O No
Painful urination?	O Yes	O No
Fever?	O Yes	O No
Foul smelling urine?	O Yes	O No
Frequent urination?	O Yes	O No
Nausea/vomiting?	O Yes	O No
Increased urge to void?	O Yes	O No

25. Did the infection occur while your child was on an antibiotic? O Yes O No
26. If yes, what antibiotic was he/she taking when the infection occured?

_____

What methods have you used to stop the badwetting?

- ☐ Rewards Yes
- ☐ Rewards No
- ☐ Punishments Yes
- ☐ Punishments No
- ☐ Ditropan (Oxybutinin)
- ☐ DDAVP pills
- ☐ DDAVP nasal spray
- ☐ Imipramine
- ☐ Nighttime Waking
- ☐ Other …

Figure 34.1B Voiding questionnaire part B.

Patient _____

Please fill out this diary for your child. Keep the diary for at least 3 days (*2 weekend days and at least 1 school day*). Record every time your child uses the bathroom, has wetting accidents, and bowel movements. Also, please record activity and fluid intake.

DATE/TIME	URINATED/PEED	WETTING ACCIDENTS	DESCRIBE ACCIDENT soaked/damp	ACTIVITY Time of accident school/sleep	FLUID INTAKE Type/Amount	BOWEL MOVEMENT Hard/soft/loose

Figure 34.2 Voiding dairy.

Primary versus secondary disorder

Whether the voiding disorder is of new onset (secondary), or the child has never been completely continent since toilet training was completed (primary), should be determined. This distinction is critical, since secondary wetting disturbances are more likely to be associated with an identifiable abnormality in contrast to children who present with primary incontinence. For example, diabetes insipidus or diabetes mellitus, PUV, and tethered spinal cord may all present with a history of secondary daytime or nighttime incontinence.[94–96] Exceptions to this rule do, however, occur. For instance, continuous dribbling of urine in some girls as a consequence of an ectopic ureter ending periurethrally may result in what appears as a primary incontinence, since these patients are never reported to be completely dry.

Bladder capacity estimation

Expected bladder capacity can be estimated, based on the interval between voids and the maximal voided volumes that have been recorded in the elimination diary. Expected bladder capacity (Figure 34.3) should be compared with calculated estimates of bladder capacity based on age, using the following formulas:[8]

Bladder capacity (ounces) less than 2 years [2 × age (years)] + 2

Bladder capacity (ounces) 2–13 years [age (years)] + 6

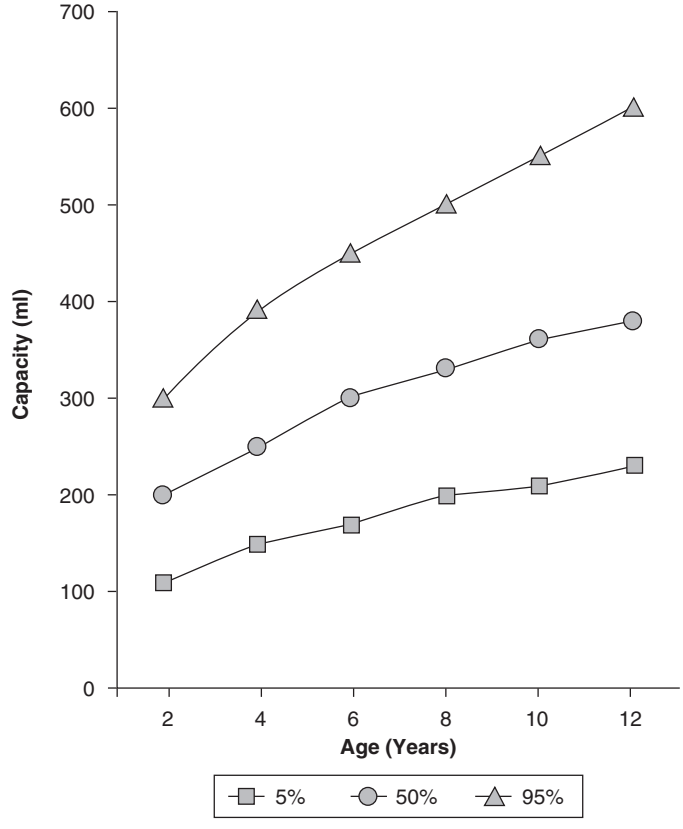

Figure 34.3 Non-linear curve showing relationship between age (years) and bladder capacity (ml). (Adapted from data of Kaefer M, Zurakowski D, Bauer SB et al. Estimating normal bladder capacity in children. J Urol 158:2261, 1997.)

Urinary stream

The characteristics of the urinary stream and events immediately preceding and following should next be noted. Children with sensory-deficient bladders do not recognize bladder filling and will typically wet themselves without recognition, often described as 'sitting in their own urine'. By comparison, the child with urgency-frequency syndrome is seen to cross their legs, squirm, grab their genitalia, or sit on one heal, in order to inhibit the detrusor contraction. A weak urinary stream in a boy may reflect PUV, whereas staccato voiding in either gender may occur because of poor relaxation of the external urinary

sphincter. Upward deflection of the urinary stream, a phenomenon seen almost exclusively in circumcised boys, occurs because of meatal stenosis. Finally, postvoid dribbling may represent release of urine pooled in the vagina on standing in girls, or from a urethral diverticulum in boys, particularly those with a prior history of urethral trauma or surgery.

Bowel function

Constipation, usually from idiopathic causes, is known to occur in as many as 10% of school-aged children.[60,97–99] Constipation has been associated with UTIs, urgency-frequency syndrome, urinary retention, incontinence, and upper urinary tract deterioration in children.[60,100,101] Significant improvement in voiding symptoms and diminished frequency of recurrent UTIs in children following specific treatment of constipation only is well documented. For this reason, it is important to inquire regarding the consistency and frequency of bowel movements, fecal incontinence, and whether prior therapy for encopresis or constipation has been attempted. However, since parents may not accurately know the bowel habits of their older children, it is often helpful to include the children in the interview by specifically asking them whether any bowel movements passed are hard, painful, or associated with blood. Since dietary factors may influence fecal consistency, and thus elimination, a detailed dietary history should also be obtained. This history should explore concomitant medication use that may predispose to constipation, such as anticholinergics, anticonvulsants, antacids, oral iron, and psychotherapeutics.

Physical examination

A comprehensive physical examination is warranted in every child with voiding dysfunction, but is most often normal. The examination should include a review of the abdomen, genitalia, perineum, anus, lower back (Figure 34.4), and lower extremity neurologic status. Palpation of the abdomen should be performed with attention to identifying constipation, which would be suggested by fullness in the lower quadrant or rectum. A palpably distended urinary bladder, particularly shortly after the child has voided, may indicate more severe voiding disturbances such as those caused by neurologic conditions, PUV, or pelvic malignancies.

In boys, when meatal stenosis is suspected, the urethral meatus should be inspected by carefully trying to spread the meatus open. If urethral mucosa is seen to evert from the meatus, stenosis is excluded. In order to confirm meatal stenosis, the child may be observed voiding: typically, the urinary stream is deflected upward in meatal stenosis, and in order to direct the stream into the toilet, the boy must aim the penis downward at an acute angle. In girls, a bifid clitoris or a urethral meatus that is patulous anteriorly is diagnostic for epispadias. An ectopic ureter to the periurethral area is suggested by continuous pooling of urine in the vaginal vault.

Rectal examination is typically not warranted in most patients with wetting. However, boys with secondary voiding dysfunction who complain of the need to strain in order to void, weak stream, and/or hesitancy should be examined rectally since these symptoms are associated with prostatic rhabdomyosarcoma. In girls, rhabdomyosarcoma presents more commonly as a vaginal introitus mass rather than with voiding complaints. Inspection of the lower back may disclose evidence of spinal dysraphism (see below). Lastly, a neurologic examination of the lower extremities may also suggest spinal cord abnormalities if loss of asymmetric strength and/or coordination is seen.

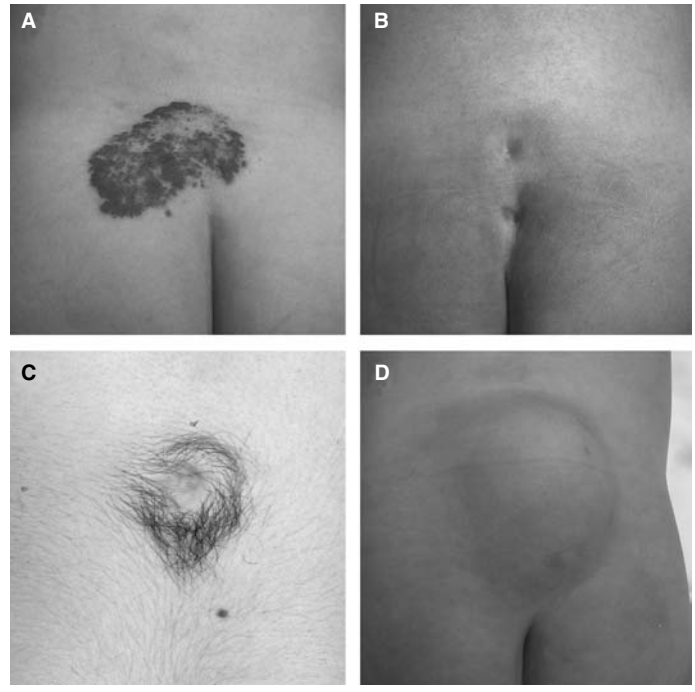

Figure 34.4 Cutaneous manifestations of spinal dysraphism: (A) hemangioma; (B) sacral dimple; (C) diastematomyelia; and (D) lipoma. (Photographs courtesy of John Myseros MD, Division of Neurosurgery, Children's National Medical Center, Washington, D.C.)

Laboratory studies

In the vast majority of cases, urinalysis with dipstick and microscopic examination provides important information regarding UTI and some metabolic disorders. When a negative dipstick analysis is combined with negative urine microscopy, infection can be excluded reliably and a formal urine culture is not warranted.[102,103]

Dipstick analysis for urinary protein, glucose, and specific gravity is helpful to screen for causes of polyuria, such as diabetes mellitus or insipidus (nephrogenic or central). Generally, a urine specific gravity measurement of ≥1.022, in the absence of proteinuria or glycosuria, indicates adequate concentrating ability.[104] Lower urine specific gravity measurements that are associated with polydipsia and polyuria should be further evaluated to exclude diabetes insipidus.

Imaging studies

Since most voiding disorders can be accurately diagnosed by clinical history only, imaging studies are rarely necessary. Pre- and postvoid RBUS is warranted in order to assess bladder emptying and to evaluate for hydronephrosis in patients with voiding abnormalities, especially if these are present in association with febrile UTI. Hydronephrosis may suggest the presence of other anatomic abnormalities, such as VUR or PUV, which can contribute to the risk of upper urinary tract deterioration in the presence of infection. In the absence of a history of febrile UTI, children do not need to have VCUG, unless other risk factors for VUR, such as a family history of reflux, are present. The advent of office-based RBUS has led some to perform this test in all children presenting with urinary incontinence; however, few children demonstrate such inefficient emptying to justify this practice.

A plain radiograph of the abdomen is helpful in demonstrating increased fecal load in children who are suspected of having constipation but who do not yield reliable information on questioning. Additionally, the radiograph also screens for occult spinal dysraphism, a rare but well-recognized cause of secondary wetting and bowel disturbances.

Screening for occult dysraphism

Rarely, unrecognized spina bifida associated with spinal cord tethering or spinal cord tumors may cause elimination disorders (see Figure 34.4). Patients known to be at risk for spinal cord tethering include imperforate anus or VATER syndrome (vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia) (up to 45%) and cloacal exstrophy (up to 100%).[105–108] These patients are easily identified, but many more subtle cases of spinal cord tethering occur in the context of spina bifida occulta.

The radiographic appearance of occult spinal dysraphisms may not be visible until after 5–7 years of age when ossification is complete.[109] This finding can be observed in as many as 30% of normal men and 17% of normal women.[109] When spina bifida occulta occurs as a bony abnormality and without cutaneous manifestations, it is considered a normal variant without clinical consequence. MRI examination of the spine is not warranted in such individuals. When cutaneous manifestations, such as a dimple or hair patch, are seen in a child with voiding dysfunction, an MRI scan should be obtained.

Any child with secondary day and night wetting, new-onset constipation, or encopresis, or children with a significant delay in toilet training, should be evaluated for occult spinal disorders. Neurologic evaluation and examination of the back for skin dimpling, hair tufts, accessory skin tags or tails, and pigmentation should be undertaken in an effort to identify spinal dysraphism. In children with gait disturbances, the relative symmetry of the gluteal muscles should also be evaluated. Finally, sensation and tone of the anal sphincter can be used as a proxy for urethral sphincter function.

Urodynamic studies

Urodynamic studies are recommended only for children with significant urinary and/or fecal elimination problems, a diagnosed posterior urethral valve, or Hinman syndrome. These patients are at risk for upper tract deterioration and may be found to have hydronephrosis and/or renal cortical scarring on presentation. The data collected from urodynamic studies should be compared with values from normal children.[110]

Treatment

In most cases, simple behavioral modification is sufficient to improve the incontinence. Surgery is rarely necessary and is only performed for severe cases of dysfunctional elimination that are recalcitrant to conventional behavioral modification or when signs of upper urinary tract changes are present. In some children, pharmacotherapy is used as an adjunct to behavioral modification.

Timed and double voiding

The establishment of regular elimination habits is of paramount importance, particularly among children who are infrequent voiders and in those whose incontinence is not associated with frequency. The child should be encouraged to void as frequently as necessary to prevent wetting based on the patterns recorded in a voiding diary. Since many of these children do not sense the need to void at lower volumes, voiding on a schedule can be associated with well-defined events throughout the day, such as waking, before meals, and before bedtime. Multi-alarm wristwatches are also helpful as auditory cues for timing of urination.

Older children may have large-capacity bladders and high postvoid residual urine volumes, and double or repeat voiding may be necessary. This can obviate the need for clean intermittent catheterization. Rarely, hydronephrosis or VUR coexists in these children and double voiding is necessary to empty the upper urinary tracts in their bladder. This 'yo-yo' pattern may be observed in children with prune-belly syndrome, bilateral high-grade VUR, and Hinman syndrome, where the upper urinary tract is highly compliant. These children should be re-evaluated by RBUS after institution of double voiding to ensure that hydronephrosis is improving. Persistent or progressive hydronephrosis and UTI reflect poor compliance with these measures and demonstrate the requirement for more intense therapy with clean intermittent catheterization.

Enuretic (wetting) alarms

Enuresis alarms worn during the day by children with daytime wetting have been reported to result in appropriate behavior modification, achieving a success rate of over 60%. Unfortunately, use of enuresis alarms during the day is more cumbersome than multi-alarm watches, which can provide similar benefit.

Bowel program

In children with associated constipation, a bowel program should be instituted to ensure that the rectum remains empty of stool.[61] Various treatment modalities can be tailored to the severity of constipation. Increasing fiber and liquid intake, bulking agents, stool softeners, and laxatives can be tried first (Table 34.2). Suppositories, enemas, and/or disimpaction may be necessary in many other cases. The recommended daily amount of fiber can be calculated using the formula:

$$\text{Grams of fiber needed per day (20 g maximum)} = \text{age (years)} + 5$$

For milder cases, dietary modification and/or fiber supplementation may follow an initial bowel clean-out using laxatives. Severe constipation may require initial manual disimpaction and rectal clean-out using enemas, followed by administration of laxatives, such as MiraLax, magnesium citrate, or polyethylene glycol electrolyte solution (GoLYTELY). In these circumstances, abdominal films obtained before and during therapy are helpful in demonstrating the fecal load. Once the clean-out phase has been completed, a maintenance phase lasting as long as 1 year should be continued with daily oral laxatives. Failure to continue these measures often results in recurrent constipation.[61]

Biofeedback techniques

Biofeedback techniques rely on combining Kegel exercises with urodynamic studies and positive reinforcement. Biofeedback has been used successfully to treat children with urinary and bowel elimination problems, recurrent UTI, and VUR,

Table 34.2 Fecal elimination regimens

	Minimal dose	Maximal dose
Bulking agents		
Fiber[a]	Age (yr) + 5 (g) per d	20 g/d
FiberCon	1 cap (6–12 yr) or 2 caps (≥ 12 yr) qd	1 cap tid (6–12 yr), 2 caps tid (≥ 12 yr)
Metamucil wafers	1 wafer bid (6–12 yr)	2 wafers tid (> 12 yr)
Senokot	1 tablet or teaspoon qd	3 tablets or teaspoons qd
Citrucel	7.5 ml in 8 oz water qd (6-12 yr) 15 ml in 8 oz water qd (> 12 yr)	7.5 ml in 8 oz water tid (6-12 yr) 15 ml in 8 oz water tid (>12 yr)
Stool softeners		
Mineral oil	1 ml/kg qd	2.5 ml/kg bid
Lactulose	1 ml/kg qd	1 ml/kg tid
Colace	20 mg/d (3–6 yr), 40 mg/d (7–12 yr), or 50 mg/d (> 12 yr) divided bid or tid	60 mg/d (3–6 yr), 120 mg/d (7–12 yr), or 200 mg/d (> 12 yr) divided bid or tid
Laxatives		
Milk of magnesia[b]	1 ml/kg qd	1 ml/kg tid
Magnesium citrate[b]	1 oz/yr of age (< 6 yr)	1 bottle (> 6 yr)
Castor oil	2.5 ml qd	50 ml qd (for adults)
GoLYTELY	8-oz glass q 20 min until recta effluent is clear	100 ml/kg or 4 L in adult-size teenagers
MiraLax[c]	5 ml in 40 oz water qd	17 g (1 heaping tablespoon in 8 oz water qd [adult dose])
Suppositories		
Glycerin	1 per rectum qd to qod	1 per rectum bid
Dulcolax	½ to 1 per rectum qd (not for chronic use)	1 per rectum bid
Enemas		
Fleet Phosphate[d]	1 pediatric dose qd	1 pediatric dose bid
Tap water[e]	100–250 ml enema qd	100–250 ml enema bid
Milk of magnesia	1:1 milk to magnesia (30–150 ml) qd	1:1 milk to magnesia (30–150 ml) tid
Fleet Mineral Oil	½ dose qd	1 enema qd

d, day; yr, year; bid, twice a day; qd, each day; qod, every other day; tid, three times a day.
[a] Dietary texts provide tables with the amount of fiber (in grams) in various foods.
[b] May result in hypermagnesemia.
[c] Advantage is no taste; safety undetermined in children; preliminary reports suggest safe in children > 2 yr of age for 6-month period.
[d] May result in hyperphosphatemia.
[e] May result in hyponatremia.

particularly when the underlying abnormality during voiding is a non-relaxing pelvic floor.[111–124]

In general, after a complete urodynamic evaluation is performed, the child's perineal muscular activity is monitored during filling and voiding by an electromyographic electrode. Pelvic floor contraction is represented by the urodynamic equipment as visual or auditory cues that the child can control. The goal is to teach the child to relax the sphincter complex completely during voiding.

McKenna and colleagues recognized how difficult it can be to maintain a child's focus during these arduous biofeedback sessions. They devised a computer game that the child controls with his/her perineal muscular activity.[122] Utilizing this method, they reported effective treatment of voiding dysfunction in 41 children with various forms of dysfunctional elimination habits. Overall, 90–100% of patients improved in all categories: 52% of nocturnal enuresis, 61% of diurnal enuresis, 33% of constipation, and 73% of encopresis patients were completely cured.

Pharmacologic therapy

Pharmacotherapy is reserved for enuresis associated with UTI or when significant social embarrassment is perceived (Table 34.3). Any child with coexisting constipation should begin a bowel program prior to the institution of any medication with anticholinergic effects, since these impair colonic motility as well. Anticholinergic and α-adrenergic medication may be contraindicated in children with closed-angle glaucoma or cardiac disease; therefore, consultation with the appropriate specialist should precede their use.

Anticholinergic agents

Anticholinergic and musculotropic medications inhibit or reduce bladder overactivity. These medications increase the threshold potential for involuntary smooth muscle cell contraction, which translates into a greater volume of urine required before the bladder contracts. The side effects of anticholinergic medication include dry mouth, facial flushing, constipation,

Table 34.3 Pharmacologic therapies available for treatment of daytime voiding disorders

Type (brand name)	Minimal dosage	Maximal dosage	Long-acting dosage
Anticholinergic			
Propantheline (Pro-Banthine)	0.5 mg/kg bid	0.5 mg/kg qid	
Oxybutynin (Ditropan)	0.2 mg/kg bid	0.2 ml/kg qid	Ditropan XL 5–20 mg qd
Hyoscyamine (Levsin)	0.03 mg/kg bid	0.1 ml/kg qid	Levsin timecap 1–2 bid
α-Adrenergic agonist			
Phenylephrine (Entex)	0.5 mg/kg bid	1 mg/kg tid	Entex LA 1 tab bid
Pseudoephedrine (Sudafed)	30 mg qid (6–12 yr)	60 mg qid (>12 yr)	Sudafed 12-hr cap bid
Ephedrine	1 mg/kg/d qid	3 mg/kg/d qid	
α-Adrenergic blockade			
Prazosin (Minipress)	0.05 mg/kg bid	0.1 mg/kg tid	
Doxazosin mesylate (Cardura)	0.5 mg/kg qhs	8 mg qhs	
Terazosin (Hytrin)	0.5 mg/kg qhs	10 mg qhs	
Smooth muscle relaxant			
Flavoxate (Urispas)	3 mg/kg bid	3 mg/kg tid	
Tricyclic antidepressant			
Imipramine (Tofranil)	0.7 mg/kg bid	1.2 mg/kg tid	
Central nervous system stimulant			
Methyphenidate (Ritalin)	5 mg before social event	10 mg before social event	Ritalin SR 20 mg qd
Dextroamphetamine (Adderall)	Non recommended		
Antibacterial prophylaxis			
Nitrofurantoin (Macrodantin)	1-2 mg/kg qhs		
Trimethoprim–sulfamethoxazole (Septra, Bactrim, Sulfatrim)	0.5 mg/kg qhs		
	0.5 mg/kg qhs		
Trimethoprim	50 mg/kg qhs		
Sulfisoxazole (Gantrisin)			

d, day; yr, year; bid, twice a day; tid, three times a day; qid, four times a day; qhs, before bedtime; qd, once daily; NR, non-recommended.

and, in hot climates, hyperpyrexia may occur. If blurred vision or hallucinations occur, it is recommended that the dose be decreased.

α-Adrenergic stimulants

α-Adrenergic agonists may be used to increase outlet resistance in patients with stress urinary incontinence. However, true stress urinary incontinence is unusual in a neurologically intact child and it is customarily found in association with an anatomic abnormality of the bladder neck, such as epispadias or urogenital sinus abnormality. Teenage girls engaged in high-impact sports have also been found to be at risk for stress urinary incontinence.

Tricyclic antidepressants

Imipramine has been the most widely used tricyclic antidepressant in children, particularly in the treatment of nocturnal enuresis. Some have reported efficacy of this class for treatment of daytime incontinence, as well. It has a dual mechanism of action, with anticholinergic effects causing detrusor muscle relaxation and α-adrenergic effects causing increased sphincter muscle activity. Tricyclics should only be used in older children and adolescents because of their relatively long half-life and risk of side effects. Anticholinergics remain the first-line therapy for daytime incontinence from detrusor overactivity, but tricyclics may be added in incrementally greater doses for refractory cases. Chlidren who require high doses of tricyclics should be monitored for cardiac conduction defects and arrhythmias with electrocardiography.

α-Adrenergic blockade

The well-documented clinical efficacy of α-adrenergic blockade to improve urinary flow and decrease postvoid residual urine volumes in men with benign prostatic hypertrophy (BPH) has led some pediatric urologists to evaluate its utility in reducing functional outlet obstruction in children with enuresis.

The rationale for the use of α-adrenergic blockade in BPH relies on evidence of α-adrenergic receptors localized to the smooth muscle cells of the bladder outlet in both genders and, especially, to the prostatic tissue in males. However, in childhood enuresis associated with poor bladder emptying, it is generally believed that diminished flow results from incomplete relaxation of the external urinary sphincter, and not as a result of increased tone of the bladder neck and/or prostatic tissues. Despite this apparent conflict, results of clinical studies using α-blocker therapy show promise.[125–127]

Three non-randomized cohort studies of a total of 88 children have demonstrated statistically significant improvements in urinary flow rate and postvoid residual urine volumes that have resulted in cessation of or diminished enuretic episodes in approximately 80% of children treated with doxazosin (0.5–1.0 mg, orally).[125–127] A major criticism of these studies has been the lack of standardized follow-up among the three studies, and inclusion of varied etiologies of enuresis, although all children had evidence of poor bladder emptying. Side effects, related to postural hypotension, are diminished by administration just prior to bedtime.

Central nervous system stimulants

Central nervous system stimulants, such as methylphenidate (Ritalin), have been used successfully to treat giggle incontinence. Children with ADHD and enuresis have also been found with diminished incontinence following institution of methylphenidate. The mechanism of action is unknown.

Pharmacotherapy for primary nocturnal enuresis

Pharmacologic therapy relies on improving functional bladder capacity through anticholinergic effects (oxybutinin, imipramine) or by diminishing nocturnal urine volume (desmopressin, DDAVP). Imipramine has been the first medication used to treat enuresis. It relies on antispasmodic effects on the bladder and stimulatory effects on the sphincter. Some data also suggest that imipramine may exert central effects that alter arousal, thus facilitating that the child awakens from sleep before enuresis occurs. Initial response rates to imipramine approximate 50%, but long-term cure rates, once the drug is discontinued, are poor (only 25%).[128]

Oxybutinin, a potent anticholinergic, may be helpful in the management of nocturnal enuresis associated with bladder overactivity. Its efficacy as a single drug used to treat enuresis is around 10–50%.[129,130] One study evaluated combination therapy with imipramine and oxybutinin.[129] Although the combination proved more efficacious in short-term results than either drug alone (90% achieved dryness), lasting results were seen in only 40% after the treatment was discontinued.

A more direct approach to enuresis appears to be improving the kidney's concentrating ability during sleep through the use of desmopressin (DDAVP). The reported response rate to desmopressin is 40–70%.[130,131] The relapse rate on discontinuation is high, with only 30% of responders maintaining continence at 1 year.[132] Desmopressin can be administered intranasally as a spray as well as an orally administered tablet.

Functional bladder capacity remains an important feature in the pathogenesis of enuresis and, if unaddressed, is likely to be associated with treatment failure. In fact, several studies have shown that functional bladder capacity is a strong predictor of response to desmopressin.[133–135] Recently, one study correlated a bladder volume and wall thickness index to the response from desmopressin and found a statistically greater likelihood of resolution when DDAVP was prescribed to children with normal bladder volume and bladder wall thickness.[136] Enuretic children with reduced bladder volume and thick bladder wall and those with large bladder volumes and thin walls had a suboptimal response to oral desmopressin.[136]

Antibiotics

Symptomatic UTI should be treated with appropriate antibiotic therapy. Prophylactic antibiotics should be considered in children with voiding disorders who suffer from recurrent infection,

since chronic inflammation may perpetuate bladder instability. Trimethoprim–sulfamethoxazole, nitrofurantoin, and trimethoprim alone have been used successfully as prophylaxis. On occasion, two antibiotics are required to adequately prevent recurrent UTI.[137]

Clean intermittent catheterization

Clean intermittent catheterization (CIC) is recommended in children who demonstrate persistently elevated postvoid residual urine volumes despite adherence to timed-voiding and double-voiding regimens, and therapy for constipation. Although children are likely to develop bacteriuria with CIC, studies have demonstrated improved continence and diminished risk for pyelonephritis and upper urinary tract deterioration.[138] CIC should be performed at 3- to 4-hour intervals. So long as complete bladder emptying is achieved regularly, bacteriuria remains clinically insignificant in the majority of these children. The use of sterile catheters is unnecessary and prophylactic antibiotics are not recommended, unless the patient has been diagnosed with VUR. In such circumstances, every effort should be made to maintain sterile urine with daily antibiotic prophylaxis. Anticholinergic medication may also be used if evidence of bladder overactivity has been found.

Endoscopy and procedures to reduce bladder outlet resistance

Historically, cystourethroscopy with urethral dilation has been used in some patients with dysfunctional voiding, based on the rationale that bladder outlet obstruction was the risk factor leading to recurrent UTIs in such girls.[139] In most treatment protocols, the urethra was dilated to 28–32 French, followed by prolonged antibiotic prophylaxis. Unfortunately, no objective clinical evidence exists that urethral dilation itself, in the absence of antibiotic prophylaxis, ever diminished the risk for UTIs.[139] This should be of no surprise, since the underlying problem in some girls with recurrent UTIs is non-relaxation of the external urinary sphincter during voiding, which is untreated by dilatation. Therefore, the abnormal voiding pattern recurs after the procedure, as does the risk for UTI.

When behavioral modification and biofeedback techniques have failed to produce sphincter relaxation during voiding, a novel surgical option has been employed to temporarily paralyze the external urinary sphincter by endoscopic injection of botulinum A toxin. Sphincter paralysis lasts between 2 and 9 months, during which the child learns to void without tightening the sphincter. As a result of improved bladder emptying, continence improves.[140]

Surgery

Surgical interventions are rarely used anymore for incontinence related to dysfunctional elimination states. Perhaps the only indication would be very high postvoid residual urine volumes, associated with upper tract deterioration, which cannot be managed by CIC, and in a patient in whom future fertility is not a concern. In those circumstances, one might consider a bladder neck incision or a Y-V plasty.

Neurologic and anatomic causes of incontinence require surgical intervention to promote continence when timed voiding and CIC have been unable to provide relief. Urodynamic studies are often helpful in determining the type of procedure to perform, such as augmentation cystoplasty, Young–Dees–Leadbetter bladder neck reconstruction, Mitrofanoff procedure, sling cystourethropexy, or placement of an artificial sphincter device. A pediatric urologist with experience in such matters should perform the evaluation of the child with severe voiding problems that have an anatomic etiology.

Concluding remarks

Incontinence, though acceptable in young children, becomes increasingly bothersome as children mature into school age. The symptom itself encompasses many disorders, both functional and anatomic. For most children who wet, a detailed history and physical examination will usually determine the type of wetting disorder and will suggest an appropriate treatment course. For these children, simple behavioral modification, such as the use of a timed-voiding schedule and dietary modification (which may also include the use of laxatives), can significantly diminish the number of wetting episodes and prevent UTI, when coexistent. When wetting presents with UTI and fever, radiologic evaluation should be performed and any underlying severe functional or anatomic abnormality rapidly addressed in order to prevent upper urinary tract deterioration.

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35 Urolithiasis

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Urolithiasis has become more common in children over the past few decades, probably due to rapid changes in society's dietary habits and socioeconomic conditions worldwide. Epidemiologic studies indicate an increasing trend of calcium oxalate and/or calcium phosphate stones in the upper urinary tract in industrialized countries, rather than the infection-related ammonium urate stones in the bladder of the past century which are now seen mostly in less affluent countries. Urolithiasis is a disorder 'shared' by the urologist and the nephrologist. The role of the urologist is to extract the stone from the urinary tract and correct anatomic abnormalities of the genitourinary tract, as indicated, whereas the role of the nephrologist is to identify the etiology for the stone and plan a management strategy to prevent stone recurrence. This chapter addresses the epidemiology, etiology, pathogenesis, clinical features, diagnostic investigation, and management of pediatric urolithiasis.

Epidemiology

Changes in global socioeconomic conditions and the subsequent changes in dietary habits have affected not only the incidence but also the site and chemical composition of calculi.[1,2] At the beginning of the last century, bladder calculus from ammonium urate was relatively frequent in Europe, but, over time, it has changed to the more common renal–ureteral calculus made up of calcium oxalate and/or phosphate, probably related to a diet rich in proteins, refined carbohydrates, and sodium, and low in potassium and citrate.[1–4] Bladder stones are still common in the developing world, whereas upper tract stones predominate in industrialized countries. The majority of bladder stones seen in developed, affluent countries are a result of bladder dysfunction or bladder reconstruction. In the United States, incidence of urolithiasis is highest among whites, especially in the 'stone belt' in the Southeast, peaking in July, August, and September. This has been linked to higher exposure to sunlight and, consequently, increased production of vitamin D and calcium absorption from the intestine on the one hand and to a higher incidence of dehydration on the other.[2] Kidney stone formation was described among lifeguards in Israel due to the same reason.[5] In recent years, an increase in pediatric urolithiasis has been observed. Lattimer and Hubbard in 1951 reported no cases of urolithiasis in 21 835 patients at the Babies Hospital in New York.[6] In later studies, the incidence of urolithiasis in children was reported as 1 in 6000 and 1 in 7600 hospitalized children.[7,8] Malek and Kelalis in 1975 described 78 cases of urolithiasis in 145 000 hospitalized children (1 in 1850); 32% of the calculi were from infection, with a greater incidence in boys (2:1 ratio) and an even distribution of patients in all age groups.[9] More recently, in 1987, Stapleton et al described 112 children with urolithiasis: 94% of these were white, 59% were boys and calcium oxalate stones predominated.[10] Milliner and Murphy observed that only 19 out of 221 children in the Mayo Clinic had bladder or urethral calculi, whereas the rest of the urolithiasis were present in the upper urinary tract and ureters, unlike the distribution in developing countries, where bladder stones are more frequent.[11] Osorio and Alon found the incidence of hypercalciuria to be significantly lower in African-American children than in Caucasian children.[12] Thus, epidemiologic studies have shown an increasing trend ('stone wave') associated with a change in social conditions and in eating habits. However, the importance of genetic predisposition, as recognized by racial distribution and family history of urolithiasis, cannot be disregarded.

Pathogenesis

Stone formation is a complex process. In a simple solution, like water, a solute will precipitate out of a solution once its saturation point, or the 'solubility product' of ions, is reached. In contrast to water, in a complex solution such as urine, a situation of 'supersaturation' of stone 'promoters' such as calcium, oxalate, and uric acid occurs due to the presence of many other ions and molecules in the urine that allow these 'promoter' ions to remain in solution even at higher concentrations. Some of the better-known substances that 'inhibit' stone formation include citrate, pyrophosphate, magnesium, and glycosaminoglycans; other inhibitors in this category that have been described in the literature are Tamm–Horsfall protein, uropontin, nephrocalcin, FKBP-12, bikunin, and lithostathine. The point at which urine will no longer hold a substance in solution is called the 'formation product', and it may also be influenced by urine pH. At the 'formation product', spontaneous nucleation takes place to form new crystals. The nucleation can be homogeneous or heterogeneous: the former refers to the joining of similar ions into crystals, whereas heterogeneous nucleation results when one crystal grows around another type of crystal, e.g. calcium oxalate crystallizing around a uric acid or cystine crystal.

Sloughed epithelial cells and other materials can also provide the nidus around which heterogeneous nucleation can occur. Thus, for stone formation or crystallization to materialize, either intermittent or continuous urinary supersaturation must occur. Supersaturation is affected by water intake and urine flow rate. High urine flow rate induced by increased fluid intake reduces urine supersaturation. This holds true for all stone types, and thus is one of the mainstays of therapy for urolithiasis. Unfortunately, a recent study showed that only a minority of children with urolithiasis adhere to high fluid intake.[13] In order to form a stone, multiple crystals need to combine together, a process called aggregation, which is believed to take place in the tubules or the collecting system. It seems that to allow this process to take place, crystals have to anchor to the urinary epithelium for a limited time, and not be washed away by urine, in a process which is yet not fully understood.[2,14] The presence of anatomic abnormalities that impede urine flow and of urinary tract infections that change the milieu in the urinary tract system are also known contributors to stone formation.

Nanobacteria that have the ability to produce carbonate apatite on their cell wall have also been implicated in stone formation. These bacteria may act as the nidi for kidney stones, and in one study were isolated from 97% of the kidney stones.[15] Thus, many factors play a role in stone formation: presence of promoters, lack of inhibitors, urine flow rates, anatomic abnormalities, nanobacteria, urinary tract infections, and homogenous or heterogeneous nucleation. All of these factors have to be considered when planning a therapeutic strategy to prevent formation of recurrent stone.

Clinical manifestations

The two most characteristic presenting symptoms of urolithiasis are pain and hematuria. Less common manifestations are urinary tract infection and acute renal failure. In other cases, stones can be detected as an incidental finding by imaging studies of the abdomen or urinary tract done for another purpose. These asymptomatic stones may at times cause obstructive uropathy.

Acute renal colic presents abruptly as a severe paroxysmal pain in waves on the affected side, associated, at times, with nausea and vomiting. The child with renal colic will usually writhe in pain or move constantly to try to find a position of comfort. The pain can occur anywhere, from the flank down to the ipsilateral groin. This visceral type of pain is caused by distention of the proximal urinary collecting system from distal obstruction, or from passage of the stone (or associated blood clot and debris). The location of the pain may give information about the possible location of the stone. Stones within the kidney or in the proximal ureter produce flank pain. As the stone moves down, the pain radiates around the front of the abdomen into the lower quadrant. Referred pain often occurs in the ipsilateral groin, testicle, and labia, as the stone reaches the ureterovesical junction (UVJ). Urolithiasis and urinary tract infection are closely related. Calculi may develop as a consequence of urinary tract infection and form struvite or carbonate apatite stones (see below). Urolithiasis places the child at risk for urinary tract infection, and the infection may be the initial presentation for stones. Presentation with urinary tract infection is more common in younger children, whereas acute renal colic is more common in older children. Lower ureter and bladder stones may present with hematuria, dysuria, or urgency, thus mimicking a urinary tract infection. Stones may also move within the ureter without any associated resistance or obstruction, causing painless hematuria, which can be either macroscopic or microscopic. The finding of hematuria with urolithiasis is relatively consistent throughout childhood. Macroscopic or microscopic hematuria has been observed in as many as 90% of children with urolithiasis.

Evaluation

At the initial visit, medical history should focus on risk factors for stone formation and its complications such as urinary tract infection, voiding dysfunction, and surgical procedures on the urinary tract. A positive family history for stone disease can be obtained in 22% (Turkey) to 75% (USA) of children with urolithiasis.[16,17] Clinical features suggestive of hereditary etiology for stone disease in childhood are shown in Table 35.1. A wide variety of medical conditions can be associated with urolithiasis in children, including gastrointestinal disorders associated with malabsorption, cystic fibrosis, myelodysplasia, and immobilization. Recurrent skeletal fractures may indicate the presence of hyperparathyroidism or other bone diseases. A history of prematurity (especially with use of furosemide), use of supplemental vitamin D, enteral or parenteral nutrition formulas high in calcium and/or phosphorus should be obtained. The dietary history must search for any dietary excesses or deficiencies, medications, vitamins, and supplements intake. Medications such as steroids, chemotherapy drugs, anticonvulsants, loop diuretics, acetazolamide, other carbonic anhydrase inhibitors, uricosuric drugs, and antacids have been associated with urolithiasis (Table 35.2). Ketogenic diets used to treat intractable seizures in children are associated with uric acid stones.[18] Excess salt and insufficient potassium intake may contribute to stone formation.[12]

Table 35.1 Clinical features indicating possible hereditary etiology of pediatric urolithiasis

Infantile or early childhood presentation
Parental consanguinity
Family history of urolithiasis
Multiple, bilateral, and/or recurrent stones
Coexistence of tubular dysfunction manifested by polyuria, acidosis, growth retardation, and/or renal failure
Presence of nephrocalcinosis
Dysmorphic and extrarenal manifestations suggestive of a syndrome

Table 35.2 Medications associated with urolithiasis

Calcium stone formation
Acetazolamide
Amphotericin B
Antacids (calcium and non-calcium antacids)
Glucocorticoids
Loop diuretics
Theophylline
Topiramate
Vitamin D
Zonisamide

Uric acid stone formation:
Acetohexamide
Allopurinol (xanthine stones)
Ascorbic acid
Benzbromarone
Calcium ipodate
Chlorprothixene
Cinchophen
Dicumarol
Estrogen
Glycerol guaiacolate
Halofenate
Iodopyracet
Iopanoic acid
Ketogenic diet
Meglumine iodipamide
Orotic acid
Outdated tetracyclines
Phenylbutazone
Phenylsulfonphthalein
Probenecid
Salicylates
Sodium diatrizoate
Ticrynafen
Zoxazolamine

Medications that may precipitate into stones
Acyclovir
Ceftriaxone
Felbamate
Indinavir
Sulfadiazine
Triamterene

Table 35.3 Normal 24-hour urinary excretion rates in children studied for urolithiasis

Volume	20–25 ml/kg/24 h
Creatinine excretion	15–20 mg/kg/24 h in adolescent male
	12–15 mg/kg/24 h in adolescent female
Creatinine clearance	>90 ml/min/1.73 m^2
Uric acid excretion	<815 mg/1.73 m^2/24 h
	<35 mg/kg/24 h
Calcium excretion	<4 mg/kg/24 h
Sodium excretion	<3 mEq/kg/24 h
Potassium excretion	>3 mEq/kg/24 h
Magnesium excretion	>88 mg/1.73 m^2/24 h
Oxalate excretion	<52 mg/1.73 m^2/24 h
	<2 mg/kg/24 h
Citrate excretion	>180 mg/g creatinine in children
	>128 mg/g creatinine in adult males
	>300 mg/g creatinine in adult females
Protein excretion	<4 mg/m^2/h
Cystine excretion	<60 mg/1.73 m^2/24 h
Urine glycolate	0.19 ± 0.07 mmol/24 h
Xanthine[a]	20–60 μmol/24 h
Hypoxanthine[a]	20–100 μmol/24 h

[a]Mayo Clinic laboratories.

Urogenital tract abnormalities predispose to the formation of infected stones. Therefore, a careful urologic evaluation of patients with infected stones is mandatory. Children on clean intermittent catheterization with a Mitrofanoff conduit, exstrophy–epispadias complex, and bladder augmentation frequently develop urolithiasis.[19–21] The examination should search for chronic diseases, including failure to thrive (distal renal tubular acidosis (RTA)), hypertension (renal disease), skeletal findings of rickets, soft tissue calcification (hypercalcemia), and abnormal external genitalia.

Urinalysis should always be part of the physical examination, and any abnormality might be a clue to the source of stone formation. Attention should be paid to urine pH and the presence of crystals; however, whereas some crystals can provide a clue to diagnosis, only cystine crystals are pathognomonic. On rare occasion, the presence of proteinuria may indicate a need to search for a tubular disorder.[22] At times, when infection related stones are suspected or as indicated by urinalysis, urine culture might be needed as well.

Laboratory and imaging studies

The laboratory evaluation is based on three components: stone analysis, biochemical profile of the urine, and blood tests. All efforts must be made to obtain the stone, either by straining the urine or by its surgical extraction. However, in many cases the stone is not caught, and in others, even if its composition is known, further analysis is needed to define the metabolic abnormality leading to its formation. For instance, calcium oxalate stones can be caused by excess calcium or oxalate in the urine, or diminished citrate, or any combination of these factors.

A timed 24-hour urine collection should be performed for volume, creatinine, calcium, sodium, potassium, uric acid, oxalate, citrate, phosphorus, magnesium, and cystine (Table 35.3). In certain circumstances, measurements may need to be done for glycerate, glycolate, 2,8-dihydroxyadenine, orotic acid, xanthine, hypoxanthine, ornithine, lysine, and arginine. In situations where it may be difficult to collect a 24-hour urine sample, random urine samples may be used (Table 35.4).

Table 35.4 Normal urine excretion rates in random urine samples corrected for urinary creatinine excretion

Calcium/creatinine (mg/mg)	<0.2
Oxalate/creatinine (mg/mg)	<0.05
Uric acid/creatinine (mg/mg)	<0.65 (10–14 years) <0.60 (14–17 years)
Uric acid/GFR	<0.56
TP/GFR (mg/dl)	4.1 ± 0.6 (12–16 years) 3.3 ± 0.3 (> 16 years)
Magnesium/creatinine (mg/mg)	>0.05
Sodium/potassium (mEq/mEq)	<2.5
Citrate/creatinine (mg/mg)	>0.18 in children >0.14 in adult males >0.30 in adult females
Cystine/creatinine (mg/mg)	<0.075
Glycolate/creatinine (mmol/mmol)	<0.013 (>12 years)
L-glycerate/creatinine (μmol/mmol)	<28

TP, tubular phosphate reabsorption; GFR, glomerular filtration rate.
Note that these values can be utilized only in children with normal muscle mass.

Table 35.5 Urinary stone composition and structure

Calcium oxalate:
- Calcium oxalate monohydrate (whewellite)
- Calcium oxalate dihydrate (weddellite)

Calcium phosphates:
- Calcium phosphate, carbonate form (carbonate apatite)
- Calcium phosphate, hydroxyl form (hydroxyapatite)
- Calcium hydrogen phosphate dihydrate (brushite)
- Tricalcium phosphate (whitlockite)

Purines:
- Uric acid
- Xanthine
- Sodium acid urate
- Ammonium acid urate
- 2,8-dihydroxyadenine
- Cystine

Others:
- Magnesium ammonium phosphate hexahydrate (struvite)
- Magnesium phosphate (newberyite)
- Acyclovir
- Indinavir
- Triamterene
- Ceftriaxone
- Felbamate
- Sulfadiazine
- Silicate
- Orotic acid

Urinary calcium excretion is increased during acute pyelonephritis and with immobilization. The 24-hour urine sample should be evaluated ideally after patients are free of stones, are free of infection, and are on their usual diet with normal fluid intake. An important component of the diagnostic urine evaluation is the assessment of urinary volume. Healthy children excrete 22.2 ± 2.0 ml/kg/day of urine, whereas children with idiopathic calcium oxalate stone invariably have a lower urine volume 12.2 ± 1.4 ml/kg/day in diagnostic 24-hour urine collections.[23] A good alternative for urine volume is to monitor specific gravity.[13] The five most common types of stones are calcium oxalate, calcium phosphate, uric acid, struvite, and cystine (Table 35.5). In areas in which calcium oxalate/phosphate stones constitute the vast majority of stones, we recommend a 'step-wise' approach to analyzing urine chemistry. First, only urine calcium excretion is assessed, while the rest of the urine sample is kept refrigerated. Only when hypercalciuria is ruled out are other chemistries analyzed.[13] The initial blood work includes tests for renal function, electrolytes, calcium, phosphorus, magnesium, uric acid, and parathyroid hormone (PTH). Subsequent blood work may be needed for vitamin D levels, enzyme assays and genetic studies, and PTH-related peptide.

Plain abdominal radiographs, by their nature, detect only radiopaque stones and have a low sensitivity (62%) and specificity (67%) for making the diagnosis of urolithiasis.[24] They – as well as the traditional intravenous pyelography – have been replaced in recent years by ultrasonography and computed tomography (CT).[2,25,26] A non-contrast spiral computerized axial tomography (spiral CT), readily available in most emergency rooms 24 hours a day, is now replacing other imaging techniques during acute episodes of urolithiasis. In patients requiring repeat studies, we recommend maximal use of ultrasonography to minimize exposure to CT-related radiation. Intravenous pyelography still remains an important imaging study for delineating complex urologic anatomy prior to surgery.

Specific stone disorders

Hypercalciuria

Hypercalciuria is the most common metabolic abnormality detected in children with stones, causing mostly the formation of calcium oxalate stones and to a lesser extent calcium phosphate stones or a mixture of the two.[13] Prior to development of kidney stones, hypercalciuria can present as frequency-dysuria syndrome, with or without microscopic or gross hematuria.[27] In a prospective study of 83 children referred for unexplained hematuria without proteinuria or previous kidney stones, 26% of children had hypercalciuria.[28] In this subset of children with hematuria and hypercalciuria, Garcia et al found persistent hematuria in 29% and persistent hypercalciuria in 70% at 1-year follow-up.[29] At 2 and 3 years follow-up, they found persistent hematuria in 38% of the children, and 61% had persistent hypercalciuria, with 17% developing kidney stones. Similarly, in a prospective study by the Southwest Pediatric Nephrology Study Group, 13% of children with hypercalciuria

and hematuria developed kidney stones within 1–4 years of follow-up.[16]

Hypercalciuria can result from genetic or acquired etiologies.[22] The gastrointestinal tract, bone, and kidneys play major roles in calcium metabolism under the influence of diet, phosphorus, fluid and electrolyte homeostasis, PTH, calcitonin, and vitamin D metabolites. Calcium reabsorption in the renal tubules is increased by PTH, volume contraction, alkalosis, and thiazide diuretics, and decreased by volume expansion, hypercalcemia, acidosis, phosphate depletion, and loop diuretics. Thus, increased calcium excretion in the urine can occur from conditions listed in Table 35.6.[22,30,31]

Although idiopathic hypercalciuria remains the commonest form of hypercalciuria, a systematic search for secondary causes of hypercalciuria should be made when clinically or biochemically suspected (see below). Idiopathic hypercalciuria has been attributed to either a defect in renal tubular reabsorption of calcium (renal hypercalciuria) or from enhanced absorption by the gastrointestinal tract (absorptive hypercalciuria). An oral calcium loading test was popular in the past to differentiate between these two forms of idiopathic hypercalciuria.[32] However, the current belief is that absorptive and renal forms of hypercalciuria may represent a continuum of a single disease, and the oral loading test to differentiate between the two entities is no longer encouraged. Aladjem et al reevaluated calcium loading tests after an interval of 3–7 years in children who were initially diagnosed as having absorptive or renal hypercalciuria and found a different result in more than half of the children studied.[33] On the other hand, they found a strong relationship between urinary sodium and calcium excretion, and suggested a detrimental role for dietary sodium in idiopathic hypercalciuria. This clinical observation has been reported by other investigators, who have also observed an inverse effect of dietary potassium on urinary calcium excretion: namely, high dietary potassium intake decreases urinary calcium excretion by an unknown mechanism (Figure 35.1).[12]

As mentioned earlier when hypercalciuria is detected as a risk factor for urolithiasis in a child, a secondary etiology should be considered since successful correction of hypercalciuria in such cases depends on eradication of the primary cause. An elevated serum calcium level should lead to evaluation for PTH and $1,25(OH)_2$ vitamin D. In the presence of normal serum calcium concentration, estimates of dietary sodium and potassium intake should be made based on urinary excretion, and measurement of serum phosphorus and tubular phosphate reabsorption per glomerular filtration rate (TP/GFR) should be obtained. An increased phosphate loss in urine stimulates synthesis of $1,25(OH)_2$ vitamin D, and causes secondary hypercalciuria from increased gastrointestinal absorption of calcium. Children who are immobilized or on long-term steroid therapy can have hypercalciuria associated with or without hypercalcemia.

One of the greatest risk factors for pediatric stone formation is a low urinary flow rate. Consequently, the management of all

Table 35.6 Causes of hypercalciuria in children

Alimentary hypercalciuria (absorptive hypercalciuria)
Idiopathic
Increased vitamin D intake
Increased (supplemental) calcium intake

Renal hypercalciuria (reabsorptive hypercalciuria)
Impaired renal calcium reabsorption:
- Idiopathic
- Distal renal tubular acidosis
- Dent disease
- Bartter syndrome
- Familial hypomagnesemia
- Familial hypercalciuria
- Use of loop diuretics (furosemide)
- Abnormalities in calcium-sensing receptor

Bone resorption (may be associated with hypercalcemia)
Immobilization
Hyperparathyroidism
Corticosteroid use
Neoplasms

Renal tubular phosphate leak

Increased vitamin D synthesis (may be associated with hypercalcemia)
Sarcoidosis
Neoplasms
Idiopathic

High dietary salt intake

Low dietary potassium intake

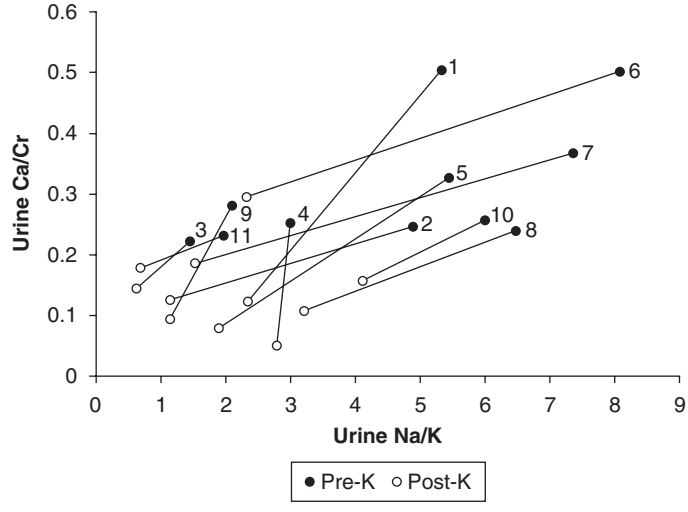

Figure 35.1 Effect of potassium therapy in 11 children with idiopathic hypercalciuria on their urine sodium/potassium and urine calcium/creatinine ratios. (Reproduced with permission from Osorio and Alon.[12])

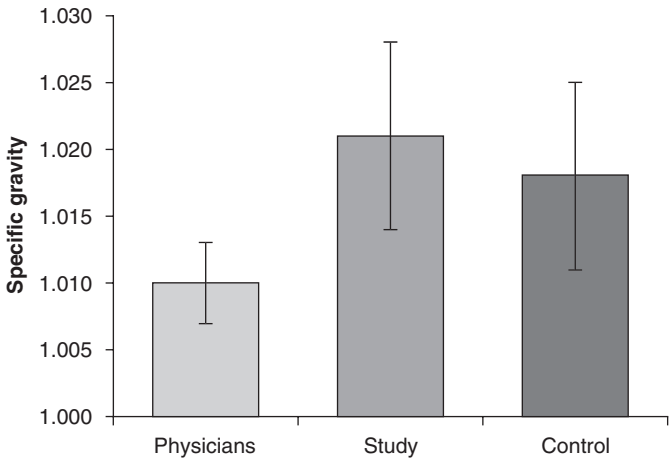

Figure 35.2 Mean (±SD) urine specific gravity recommended by physicians vs readings in children with urolithiasis and control children. (Reproduced with permission from Alon et al.[13])

patients with urolithiasis starts with recommendation to maintain a high oral fluid intake, aimed at reaching a urine output of approximately 35 ml/kg/day. A good way to monitor compliance is to assess urine specific gravity during clinic visits. Most pediatric urologists and pediatric nephrologists recommend maintaining a specific gravity at or below 1.010.[13] Unfortunately, we recently showed that adherence with this recommendation is very poor (Figure 35.2). When idiopathic hypercalciuria is confirmed, the next step is to assess whether dietary manipulation can normalize calcium excretion. We recommend a diet of RDA (recommended daily allowance) for protein and calcium that is not excessive in salt (2.0–2.4 g of sodium per day), supplemented with at least the RDA of five servings of fruits and vegetables (3.0–3.5 g of potassium per day) (Table 35.7). Indeed, currently only a minority of children in the USA adhere to the RDA of fruit and vegetable intake.[34] Compliance with these dietary recommendations can be assessed by measuring the urine Na/K ratio, which should be <2.5 (see Table 35.4). If in 4–6 weeks hypercalciuria persists, treatment with potassium citrate at 1–1.5 mEq of potassium/kg/day is recommended. If the child does not tolerate potassium citrate or fails to correct hypercalciuria, a thiazide diuretic can be added.[13] Another potential reason, although not yet fully substantiated, to convert from potassium citrate to thiazides is in patients developing highly alkaline urine, which, by itself, may promote calcium phosphate stones.[35] Chlorothiazide 15–25 mg/kg/day or hydrochlorothiazide 1.5–2.5 mg/kg/day can be used. Children on long-term thiazide diuretics will need to be monitored for dyselectrolytemia, hyperlipidemia, and hyperglycemia. The addition of amiloride might further enhance the anticalciuric effect and protect from hypokalemia.[36] Dietary restriction of calcium is not recommended, as it puts the growing child at risk for negative calcium balance and poor bone mineralization. It may also increase urinary excretion of oxalate from the increased gastrointestinal absorption of oxalate that results from decreased luminal availability of calcium to bind with it. For the same reasons, drugs such as sodium cellulose phosphate, which act by complexing intestinal calcium, are not used in children. Neutral phosphate can be used in children with hypercalciuria due to tubular phosphate leak. In children with hypercalciuria secondary to RTA, potassium citrate is the drug of choice for treatment of hypercalciuria. At times, this may need to be supplemented by sodium bicarbonate and calcium-sparing diuretics.

Hypocitraturia

A decrease in urinary citrate excretion is an important factor in the genesis of urolithiasis, particularly in the form of calcium oxalate stones. Hypocitraturia can be either idiopathic, secondary to systemic acidosis or hypokalemia, or associated with various bowel diseases. Systemic acidosis and hypokalemia are believed to impair citrate synthesis and increase renal resorption, resulting in hypocitraturia. Thus, a finding of decreased urinary citrate excretion should alert the clinician to the possibility of distal or incomplete RTA, and evaluation of urine–blood PCO_2 following oral acetazolamide should be carried out.[37] In addition, a subtle renal acidification defect can also occur secondary to renal tubular injury from chronic hypercalciuria and urolithiasis.[38] Naturally, in patients with acidosis or hypokalemia, the electrolyte abnormalities should be corrected. Potassium citrate is the rational drug of choice in children with reduced urinary citrate excretion as well as in those with hypercalciuria and hyperuricosuria, with close monitoring of urine pH. A diet rich in fruit and vegetable is recommended to enhance urine potassium and consequently citrate excretion[31] (Figure 35.3).

Hyperoxaluria

Under normal circumstances the majority of oxalate that appears in the urine is derived from endogenous production, with almost equal contributions from ascorbic acid metabolism and glyoxylate metabolism. Only 10–15% of urinary oxalate is believed to originate from the diet. Mild hyperoxaluria can be either idiopathic, or secondary to an enteric hyperoxaluria from fat malabsorption. Mild hyperoxaluria can be observed in adolescents who develop food fads rich in vegetables (with high oxalate content), high in vitamin C, or poor in pyridoxine (which leads to build-up of glyoxylate). In enteric hyperoxaluria, excess fat in the gastrointestinal lumen binds to luminal calcium, which makes the latter unavailable to bind dietary oxalate, leading to increased gastrointestinal absorption of oxalate. Absence of the anaerobic intestinal oxalate-degrading bacterium *Oxalobacter formigenes* may also play a role in some cases of secondary hyperoxaluria, as has been shown in cystic fibrosis patients, in whom the development of renal stones is quite common.[39]

Moderate to severe hyperoxaluria is observed in primary hyperoxaluria type I and type II. In type I, the more prevalent

form, the genetic mutation is in alanine–glyoxylate aminotransferase, resulting in increased urinary excretion of oxalate, glyoxylic acid, and glycolic acid. Once renal failure has developed, this leads to recurrent urolithiasis, nephrocalcinosis, renal failure, and systemic oxalate deposition (oxalosis). In type II, a rare entity, the defect is in the D-glycerate dehydrogenase enzyme, resulting in increased urinary excretion of oxalate and L-glycerate.

In children with urolithiasis associated with hyperoxaluria, a low oxalate diet is recommended (see Table 35.7). In cases of secondary hyperoxaluria due to fat malabsorption, a fat-restricted diet supplemented by increased calcium intake is also recommended. As most individuals with inflammatory bowel disease also have low urine citrate levels, potassium citrate can be added as well. In primary hyperoxaluria, a trial of treatment with pyridoxine is warranted. Reduction of oxalate production by pyridoxine is effective in some children with primary hyperoxaluria in reducing the urinary excretion of oxalate. Recent studies show that only those children with certain mutations will benefit from pyridoxine therapy.[40,41] The starting dose is 10 mg/day, and may be increased gradually to 100 mg/day. Magnesium, citrate, pyrophosphate, and thiazide diuretics in combination can also be utilized in children with primary hyperoxaluria. In severe cases with systemic oxalosis, dialysis and liver–kidney transplantation may be required.

Uric acid

Uric acid stones account for 2–4% of urolithiasis in children. In contrast with calcium stones, uric acid stones are radiolucent. The excretion of uric acid is found to be increased in some children with hypercalciuria, and thus may serve as a nidus for

Table 35.7 Dietary considerations in children with urolithiasis

High potassium	High oxalate	High purines
Fruits and fruit juices: Apricots Avocado Banana Cantaloupe Grapefruit juice Honeydew melon Kiwi fruit Nectarine Orange Orange juice Pear Prune juice Raisins Tangerine juice Tomato juice V-8 juice Vegetables: Broccoli Brussels sprouts Carrots Corn on the cob Lettuce: romaine, butterhead Mushrooms Potato Squash Succotash Tomato Dairy products: Cottage cheese Ice cream Milk Yoghurt	Beets Berries: blackberries, blueberries, strawberries, raspberries, currants, gooseberries Celery Chocolate Cocoa Cranberry juice Dried figs Gelatin Grape juice Green beans Green onions Grits Leafy greens: collard greens, dandelion greens, swiss chard, spinach, escarole, mustard greens, sorrel, kale, rhubarb Leeks Nuts Okra Pepper Summer squash Sweet potatoes Tea Tofu (bean curd)	Alcohol Asparagus Cauliflower Chickoo Custard apple Dry beans (lentils, lima, and kidney beans) Fish: anchovies, sardines (canned), herring, mackerel, cod, halibut, tuna, carp Gravies Meat extracts: bouillon, broth, consommé, stock Meat: beef, pork, lamb, poultry Mushrooms Organ meats: kidney, liver, pancreas, brain, heart Peas Pulses Shellfish Spinach Sweet breads Tea and coffee

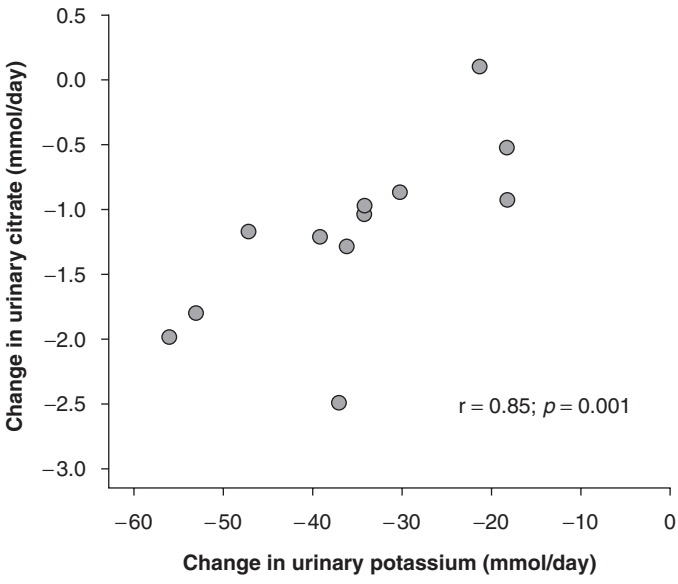

Figure 35.3 Effect of change in urine potassium excretion on urine citrate excretion. (Reproduced with permission from Meschi et al.[31])

development of calcium oxalate/phosphate stones. In children older that 2 years of age, the normal urine acid excreted per GFR value is < 0.56 mg/dl:

$$\text{Uric acid/GFR} = U_{\text{Uric acid}} \times S_{\text{Creatinine}}/U_{\text{Creatinine}}$$

In addition, Matos et al have published age-related nomograms of random urine uric acid/creatinine ratios, which are higher in infancy and decrease as the child grows older (Figure 35.4).[43]

An increased urinary uric acid excretion may result from increased glomerular load of uric acid (from excessive dietary purine intake, hematologic/myeloproliferative disorders, or metabolic errors such as Lesch–Nyhan syndrome, glycogen storage disease type 1, etc.), or from isolated or generalized tubular defects. In a child with uric acid stones and hyperuricemia, an evaluation for the purine salvage enzymes hypoxanthine – guanine phosphoribosyl transferase (HPRT) and phosphoribosyl pyrophosphate synthetase (PRPS) should be made.[44] Complete HPRT deficiency results in Lesch–Nyhan syndrome, in which the afflicted males suffer from severe neurologic abnormalities in addition to recurrent uric acid calculi.

Urolithiasis associated with increased urine uric acid in the face of low or normal serum uric acid can occur from a primary tubular defect in uric acid handling by the kidney (as in hereditary renal hypouricemia, hereditary hypouricemia with hypercalciuria, and osteoporosis), secondary generalized tubular disorders, or iatrogenic administration of various uricosuric drugs (see Table 35.2).

In a significant number of patients with uric acid urolithiasis, urinary uric acid excretion may be normal. The culprit in these cases is persistent low urinary pH. Urine pH plays an important role in uric acid urolithiasis, as uric acid crystals are poorly soluble in acidic urine and precipitate easily. This is best exemplified by development of uric acid urolithiasis in children on

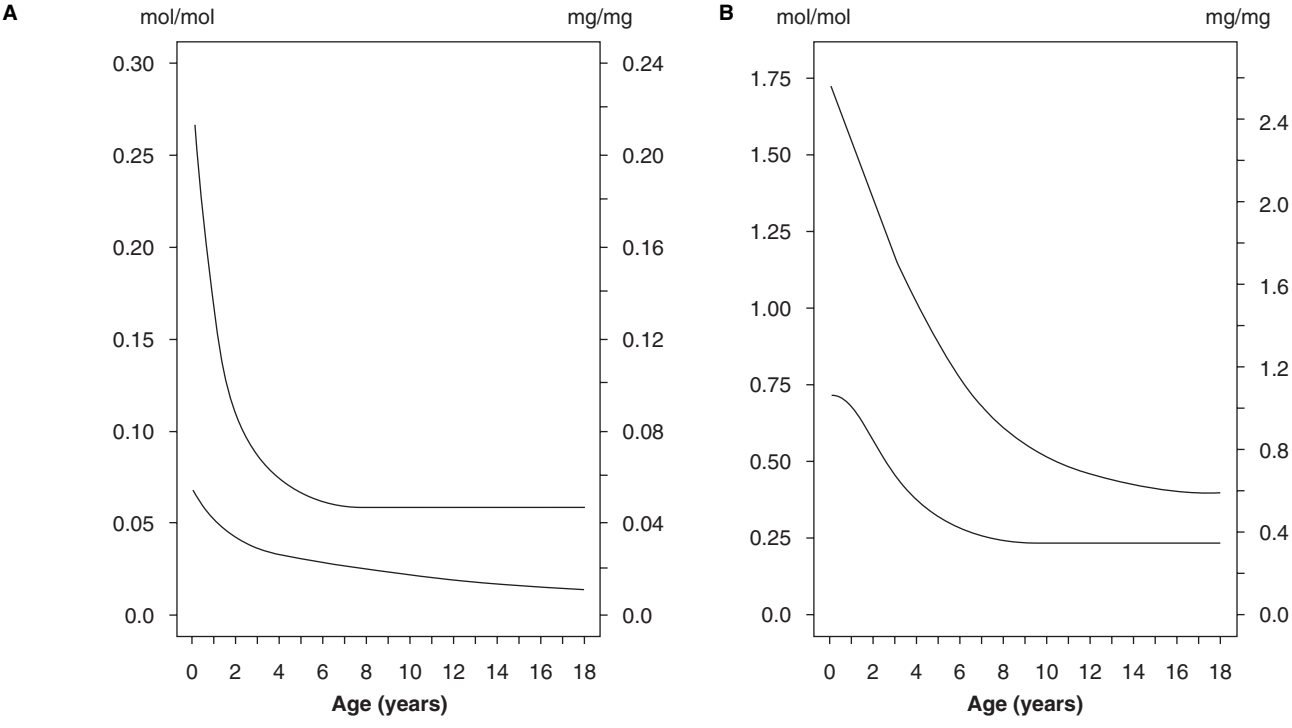

Figure 35.4 Fifth and 95th percentile of urinary (A) oxalate/creatinine and (B) uric acid/creatinine ratios in normal children. (Reproduced with permission from Matos et al.[43])

ketogenic diets for intractable seizures. Despite normal urinary uric acid excretion, the systemic acidosis leads to a constantly low urine pH and hypocitraturia. This is further worsened by poor fluid intake and prolonged immobilization, which lead to stone formation.[18] Interestingly, recent studies have found an association between uric acid stones and overweight and insulin resistance causing low urine pH due to decreased ammonia production.[45] The therapy for uric acid calculi in most patients includes efforts to alkalinize the urine to a pH of 6.5–7.0 with potassium citrate, and to maintain a high urine flow rate. A diet low in purines is recommended. This includes restrictions on red meat, fish, fowl, coffee, cocoa, chocolate, sardines, and cakes with a high yeast content (Danish pastries for instance) (see Table 35.7). In cases of increased uric acid production, the use of allopurinol may be required.

2,8-Dihydroxyadenine calculi

Deficiency in adenine phosphoribosyl transferase (APRT) is an autosomal recessive disorder leading to formation of excessive 2,8-dihydroxyadenine. These calculi are hard to distinguish from uric acid stones, and specialized chemical analysis is required to distinguish between the two. These children generally have normal levels of uric acid in the serum and urine. At times, a clue to diagnosis is the presence of brownish crystals on the baby's diaper. The suspicion is that 2,8-dihydroxyadenine urolithiasis is underreported, since most of these patients are incorrectly suspected of having uric acid lithiasis and respond to allopurinol (which eliminates the lithogenic 2,8-dihydroxyadenine from the urine). Thus, the correct diagnosis is often missed. The importance of correct diagnosis relies on the fact that alkalization of urine indicated for uric acid stones decreases the solubility of 2,8-dihydroxyadenine and thus increases the risk for urolithiasis. A low purine diet is also recommended. Thus, presentation with a uric acid-like stone without increases in serum or urine uric acid excretion, or presence of other factors predisposing to uric acid calculi formation, may require evaluation for a 2,8-dihydroxyadenine stone.

Xanthine stones

Xanthine stones occur primarily from a deficiency in the enzyme xanthine dehydrogenase and secondarily from allopurinol therapy, which inhibits the enzyme. In hereditary xanthinuria, the enzyme deficiency results in an inability to degrade hypoxanthine and xanthine to uric acid. Uric acid is virtually undetectable in plasma and urine on a purine-free diet and is replaced in the urine by xanthine and, to a lesser extent, hypoxanthine in the ratio of 3–4:1. Xanthine calculi should be suspected when orange-brown sediment is noted in the urine. Xanthine stones are radiolucent. There is no specific therapy for xanthine stones other than increased fluid intake. Special attention should be given to maintaining dilute urine during the night. In cases of secondary xanthine stones due to allopurinol therapy, as in children with Lesch–Nyhan syndrome, consideration should be given to lowering the dose of allopurinol to allow the highest tolerated concentration of uric acid, which can be controlled by concomitant urinary alkalinization and lessening the xanthine load (as xanthine solubility is almost unaffected by urine alkalinity).

Cystinuria

Cystinuria is an autosomal recessive disorder characterized by increased urinary excretion of cystine and other dibasic amino acids (ornithine, lysine, and arginine). Cystinuria accounts for 2–4% of children with kidney stones in developed countries. A higher incidence may be encountered in areas endemic for consanguinity. Cystine stones are usually, but not always, radiopaque due to the presence of sulfur ions, and occasionally, may have a component or serve as a nidus for calcium oxalate stone. One study showed that cystinuria can be associated with hypercalciuria (18%), hyperuricosuria (22%), and hypocitraturia (44%), probably caused by renal tubular acidification defect.[46] Cystine crystals appear as flat, hexagonal, and colorless, and should be searched for in concentrated acidic urine. Normal individuals excrete < 60 mg of cystine per 1.73 m^2 of body surface area per day, whereas patients who are homozygous for cystinuria often have excretion rates > 400 mg/1.73 m^2/day. Patients with non-specific proximal renal tubular aminoaciduria may excrete as much as 200 mg of cystine/ 1.73 m^2/day. The solubility of cystine in urine is about 250 mg/L, up to pH 7.0, and rises sharply with higher pH, up to 500 mg/L or more above pH 7.5.[47] The treatment goal in this condition is to maintain a high fluid intake of 1.5–2.0 L/m^2/24 hours to maintain a urinary cystine concentration of < 300 mg/L. The fluid intake should be distributed throughout the day and night. More than in any other stone disease, nocturnal diuresis is of crucial importance. Patients should ideally drink a large amount of water before going to sleep and get up at least once at night to void and have additional water intake. Furthermore, the urine needs to be alkalinized to a pH of 7.5. To attain a urinary pH of 7.5, the daily alkali dose of sodium bicarbonate or potassium citrate can reach 3–4 mEq/kg/day. Patients should be instructed to monitor their urinary pH and to maintain pH between 7.0 and 8.0. As cystine excretion correlates with dietary sodium intake, a low salt diet is indicated, combined with a high fruit juices (mostly citrus) intake. The latter contain citric acid and potassium, thus increasing both diuresis and alkali load.

In children in whom hydration, decreased salt intake, and urinary alkalinization have failed, D-penicillamine or α-mercaptopropinyl glycine may be used. Both of these compounds are sulfhydryls; they cleave cystine into two cysteine moieties to form mixed disulfides, which are 50 times more soluble than cystine. D-penicillamine is administered at a dose of 20–50 mg/kg/day in divided doses, with half of the daily dose taken at bedtime, as urinary cystine concentration is maximal during the night. The dose for α-mercaptopropinyl glycine is 15 mg/kg/day. The therapy should be supplemented with

pyridoxine hydrochloride (vitamin B_6) 25–50 mg/day, due to the antipyridoxine effect of the drug. The adverse effects of D-penicillamine include skin rash, fever, lymphadenopathy, and loss of taste. Proteinuria may develop after several months of treatment and may progress to nephrotic syndrome, which improves on discontinuation of therapy. Because of the potential for serious toxic effects associated with its long-term use, it is recommended to either discontinue therapy or maintain only the bedtime dose as prophylaxis when calculi are no longer present. Captopril, which is a sulfhydryl agent, has been used with mixed results in cystinuria.

Infection-related urolithiasis

Infection-related stones constitute approximately 2–3% of the stones in children and are more common in young children. 'Infection stone', 'infection-induced stones', and 'triple-phosphates stones' are all synonymous terms that refer to magnesium ammonium phosphate or struvite [$MgNH_4PO_4 \cdot 6H_2O$] and carbonate apatite [$Ca_{10}(PO_4)_6CO_3$] stones. The formation of struvite stones require an alkaline urinary pH, which is provided by breakdown of urea by uropathogens, such as *Proteus* and *Staphylococcus aureus*, and less commonly *Klebsiella*, *Serratia*, *Pseudomonas*, and *Staphylococcus epidermidis* which produce urease. Abnormalities of the genitourinary tract, especially presence of obstruction, predispose to the formation of infected stones. Infection with these organisms sometimes produces a soft radiolucent mucoid substance called a 'matrix concretion', which may calcify rapidly into a radiopaque stone and account for some of the rapid formation of struvite stones seen in clinical practice. These stones can completely fill and form a cast of the pelvocalyceal system and are known as 'staghorn calculi'; they have the potential to cause severe urinary obstruction, pyelonephritis, and urosepsis. One of the essential management strategies in infection-related stone is to sterilize the urinary tract. As with any other infected foreign body, surgical removal of the offending agent may become necessary to sterilize the biologic system. Staghorn calculi in children must invariably be removed and, rarely, nephrectomy may be required. In some selected cases, irrigation with hemiacridin or buffered citrate to dissolve struvite stones has been used. Acetohydroxamic acid is a urease inhibitor that has been used to reduce production of urinary ammonia and carbon dioxide to decrease struvite stone formation; it does not dissolve the struvite stones once they are formed. It has been used effectively in adults, but has been limited by its psychoneurologic and musculo-integumentary side effects, and, therefore has not yet been approved for use in children.[48] With improved management of both pediatric obstructive uropathy and urinary tract infections, infection-related stones are rarely seen nowadays in industrialized countries.

Idiopathic stones

In a number of children in whom a stone is not retrieved, routine urine chemistry analysis may be normal. In such cases, an investigation for less common etiologies such as hypomagnesemia should be carried out. If still normal, we recommend (as a first step) only non-pharmacologic interventions, including high fluid intake and an appropriate diet (see below). On rare occasions, the addition of potassium citrate is needed. We believe that this is because although each of the individual biochemical variables – such as calcium, uric acid, oxalate, and citrate – may still be within the normal range, under certain condition their product(s) may exceed supersaturation.

Management

Renal colic requires symptomatic treatment with quick pain control (narcotic analgesics), hydration (oral or parenteral flow rate equaling 1.5–2.0 × maintenance), and prophylactic antibiotics (after appropriate cultures have been obtained). Children need to be admitted to the hospital if they have intractable vomiting, intractable pain, urinary tract infection with obstruction, single kidney, or transplanted kidney. After resolution of renal colic, a course of expectant observation may be recommended for small (< 4 mm) distal ureter or non-obstructed renal stones, while urine is strained for stone retrieval. Stones ≥ 4 mm in diameter rarely pass spontaneously and usually require surgical intervention.[49] In adults, combination treatment with nifedipine and corticosteroids may enhance stone expulsion.[50] In cases of stones causing intractable pain, large obstructing stones, or anuria (solitarily functioning kidney or bilateral stones), urgent surgical treatment is necessary.

One of the greatest risk factors for pediatric urinary stone formation is a low urinary flow rate. A high fluid intake is critical in preventing supersaturation of the urine, regardless of the etiology of urolithiasis. Children with urolithiasis have a lower diagnostic 24-hour urine volume than normal children.[23] We recommend that children drink enough fluids to have urine that has no color to it. We advise the family to prepare daily, in advance, the fluids the child needs to consume, with an optional reward system.

Based on epidemiologic observations, there is no doubt that diet plays a role in urolithiasis.[1] Robertson and Peacock showed that the increased consumption of animal protein in Leeds and in the UK correlated with an increased incidence of calcium oxalate stones in the population.[4] Borghi et al showed that in men with recurrent calcium oxalate stones and hypercalciuria, restricted intake of animal protein (54 g/day) and salt (50 mmol/day), combined with a normal calcium intake (30 mmol/day), provides greater protection than the traditional low-calcium diet (10 mmol/day).[51] Curhan et al showed that high intake of phytate, which is present in fruits, vegetables, and whole grains, lowered the risk of kidney stones in younger women.[52] Shuster et al showed that subjects who consumed more than 160 ml of phosphoric acid-containing soft drinks at the time of diagnosis of a stone had a significantly higher recurrence-free interval if the soda was discontinued.[53] Thus, it appears that the more we deviate from a traditional balanced

diet with normal intake of protein, salt, fruits, and vegetables, and supplement them with rich fast foods and artificial drinks, the more we increase our risk of urolithiasis. Therefore, a diet with RDA protein and calcium intake, low in sodium and oxalate and rich in potassium, is recommended for children with hypercalciuria, oxaluria, and idiopathic stones. In adults, higher dietary magnesium intake was also found to have a beneficial affect in preventing stone formation.[30]

Role of surgery

A surgical approach may be necessary in children with obstructive or infected urolithiasis. The factors that must be taken into account when selecting the choice of surgical therapy for urolithiasis depend on the size of the calculus, its location and composition, and the associated urinary tract anatomy. The surgical approach to urolithiasis may consist of extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), endoscopic extraction, an open surgical approach, or a combination of these different techniques.[54]

Extracorporeal shock wave lithotripsy is now frequently being used in children with urolithiasis. Urolithiasis from uric acid and calcium oxalate dihydrate calculi are most responsive to ESWL; calcium oxalate monohydrate, struvite, and brushite are more difficult to fragment, whereas cystine calculi are resistant to ESWL. ESWL has a good success rate and is applicable in almost 80% of the pediatric stones. Its role may be still limited in children with large calculi, lower pole stones, and stones in an anatomically abnormal urinary tract.[55] ESWL is safe and effective, with very little difference in success rates among different lithotriptors. Although renal blood flow is reduced transiently following ESWL, no significant decrease in mean ipsilateral and total GFR, or long-term lesion on DMSA renal scans has been identified in children undergoing ESWL.[56,57] The common side effects observed with ESWL are renal or perinephric hematoma, post-treatment flank pain, gross hematuria, and trauma to extrarenal tissues lying in the blast path, such as skin bruising at the entry site of the shock wave and pulmonary (infiltrates, contusion, and hemoptysis).

Percutaneous nephrolithotomy can be used alone or in combination with other surgical techniques in the management of urolithiasis. It is especially useful in children with a large stone burden, orthopedic rods for spine stabilization, or a history of renal surgery. A percutaneous access to the renal pelvis is established and a rigid or flexible nephroscope is used to manipulate the calculi. Currently, available nephroscopes can accommodate laser, electrohydraulic or ultrasonic probes, grasping forceps, and/or basket extractors. The calculi can then be broken down and extracted. The procedure carries the risk of significant blood loss, requiring transfusion and possible urosepsis. Similarly, endoscopic procedures using ureteroscopes and/or cystoscopes can be used to remove a calculus using basket retrieval, grasping forceps, electrohydraulic, ultrasonic, or laser lithotripsy. Open surgery is required for calculi that are not amenable to ESWL, PCNL, or endoscopic techniques. In children with severe stone burden, complex urinary anatomy, or previous surgical procedures, a combination of the above techniques may be used together or in succession.

Outcome

The literature suggests that 50% of adults will have a recurrence within 10 years, depending on the type of urolithiasis. Noe, on follow-up of 27 of 44 children with hypercalciuric stones, found that 9 (33%) developed a recurrence 3–15 years after the initial episode (mean 7.2).[58] There was a significant association with a positive family history of stones in first-degree relatives. Hypercalciuria was the main risk factor for recurrence of stones with or without structural abnormality. In a randomized controlled study, Soygur et al have shown that 60 mEq/day of potassium citrate given to adults with calcium oxalate stones after ESWL significantly reduced the recurrence rate.[59] Thus, the benefits of potassium citrate and/or thiazide therapy have to be weighed against the risk of long-term use of these medications, especially in children presenting with first-time idiopathic stone. We therefore emphasize the need to develop healthy eating and drinking habits in all children with stones, and consider drug therapy only in children in whom we can identify an underlying metabolic disorder or children who develop recurrent stones.

Acknowledgments

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36 Urinary tract infection

Barbara Jantausch and Kanwal Kher

Urinary tract infection (UTI) is a common childhood infection, being only second in frequency to those of the respiratory tract. In many children, these infections occur recurrently, causing significant morbidity, hospitalizations, and long-term health impacts, such as renal scars, hypertension, and chronic renal failure. While bacterial UTIs caused by enterococci are well recognized in children and adults, fungal, viral, and parasitic infections of the urinary tract are also encountered with an increasing frequency, especially in immunocompromised and susceptible subpopulations.

Epidemiology

The true prevalence of UTI in children is difficult to estimate. Large-scale urinary screening studies of school children suggest the incidence of bacteriuria, mostly in asymptomatic children, to be 0.7–1.95% in girls and 0.04–0.2% in boys.[1,2] Kunin et al estimated that 5% of girls would develop bacteriuria by the time they graduate from high school.[2] Lifetime risk of symptomatic UTI is 3–5 times higher in girls than in boys. In numerous epidemiologic studies, the overall risk for UTI has been reported to be 1.1–1.8% in boys and 3.3–7.8% for girls.[3–5]

In the first 3 months of life, UTI is more common in males than in females. The male:female ratio of children with UTI in this age group ranges from 2:1 to 5:1.[6–8] The reasons for male predilection for UTI in neonates remains unclear, but follows a similar trend noted for other infections and sepsis in this age group. Bacteremia associated with UTI is also common in neonates and young infants. Ginsburg and McCracken reported the incidence of bacteremia in hospitalized infants < 8 weeks old with UTI to be as high as 31%.[9] Other clinicians have reported a lower incidence (~10%) of bacteremia in unselected non-hospitalized infants with UTI.[10]

Bacteriology

Gram-negative enteric bacteria of the Enterobacteriaceae family cause most UTIs in children of all ages. This includes *Escherichia coli*, which are responsible for 80–85% of all UTIs among children. *Klebsiella*, *Proteus*, and *Enterobacter* spp. and *Morganella morganii*, and the other members of the Enterobacteriaceae family are less frequent causes of UTI.[9,11,12] Less commonly, *Pseudomonas aeruginosa*, Gram-positive organisms such as *Enterococcus* and *Staphylococcus*, and *Group B Streptococcus* also cause UTI in children. *Group B Streptococcus* is almost exclusively seen as a cause of UTI in neonates, whereas *Staphylococcus saprophyticus* is typically seen in adolescent girls.[13] In one study of UTI in college women, *S. saprophyticus* was the second most common uropathogen isolated (11%) after *E. coli* (79%).[14] *Staphylococcus aureus* is an uncommon cause of UTI and may be the result of hematogenous spread to the kidney. Infection with *S. aureus* often results in focal renal lesions, such as intrarenal and perinephric abscesses.[15,16]

Pathogenesis

Our understanding of the pathogenesis of UTI represents evolution of scientific knowledge over the last several decades. Infection can reach the urinary tract via the ascending route, or by the hematogenous route. Hematogenous spread of infection to the urinary tract accounts for less than 1% of UTIs, and commonly occurs in states of sepsis, particularly due to *S. aureus*.[15,16] Resultant infection leads to focal renal lesions, such as pyelonephritis, intraparenchymal abscess, and perinephric abscess. In most cases, UTI results from an ascending infection, where the Gram-negative enteric flora ascend via the urethra to invade the urinary tract and cause asymptomatic bacteriuria, acute cystitis, or acute pyelonephritis in the host.

Predisposition to UTIs can result from structural abnormalities of the urinary tract, such as vesicoureteral reflux (VUR), or from functional derangements of the bladder. Identification and treatment of these underlying disorders is an essential component of the therapeutic plan for the affected child. Virulence of the infecting organism is also important in establishing the infection within the host urinary tract.

Bacterial virulence factors

Specific microbiologic properties of *E. coli*, known as virulence factors, are now recognized to be involved in enhancing

the invasiveness of these organisms. Strains possessing these virulence factors are able to spread to the urinary tract and result in more serious infections.

Adhesins or fimbriae

Adhesins, or fimbriae, are microscopic appendages present on the surface of *E. coli* that allow bacterial adherence to the uroepithelial cell.[17] Fimbriae allow *E. coli* to bind to specific glycolipid receptors on uroepithelial cells and permit evasion of host defense mechanisms. Type I fimbriae, Type II fimbriae–also known as P fimbriae, and the Dr hemagglutinin are three types of clinically significant fimbriae expressed by uropathogenic *E. coli*. Type I fimbriae exihibit mannose-sensitive hemagglutination, and attach to bladder epithelial cells.[18] P fimbriae demonstrate mannose-resistant hemagglutination, and are associated with acute pyelonephritis.[19] *E. coli* that express the Dr hemagglutinin, a fimbria-like adhesin, are associated with the development of cystitis.[20.]

Hemolysin and cytotoxic protein

E. coli strains that produce hemolysin, a cytotoxic protein that lyses erythrocytes and other cells, are associated with the development of acute pyelonephritis. Similarly, strains which produce colicin, another cytotoxic protein, have increased virulence and can cause pyelonephritis.[21–23]

Serotypes and bacterial virulence

E. coli contains three major antigens that are identified through antibody serotyping and are associated with invasiveness and virulence of the strain:

- the O antigen, which is present in the outer membrane of the cell wall
- the K antigen, or the capsular antigen
- the H antigen or the flagellar antigen.

More than 150 O antigens and in excess of 50 K and H antigens have been identified.[24] *E. coli* strains with certain O antigen serogroups (1, 2, 4, 6, 7, 8, 16, 18, 25, and 75) are associated with the development of pyelonephritis.[25,26]

Bacterial genetics

The virulence of uropathogenic *E. coli* is attributed to the presence of multiple bacterial virulence factors: i.e. toxins, adhesins, or specific O antigens. Many of the genes encoding for these virulence factors are located on distinct pieces of DNA called pathogenicity islands (PAIs) that are present in the genome of pathogenic bacteria and are not found in avirulent bacteria strains. Genes encoding for hemolysin or P-fimbriae production are characteristically found in PAIs. PAIs can be deleted from the chromosome, and can also be transferred to other bacteria by helper phages.[27,28]

Host inflammatory response

The inflammatory response generated by the host in the kidney and the urinary tract to the invading bacteria is an essential determinant of the severity and outcome of UTI.[29] Once uropathogenic *E. coli* attach to uroepithelial cells, they initiate inflammation by stimulating uroepithelial cells to produce cytokines and chemokines, such as interleukin-6 (IL-6) and interleukin-8 (IL-8).[30,31] Urinary IL-6 and IL-8 concentrations are elevated in the urine of children with urinary tract infection.[32,33]

Infection with P-fimbriated *E. coli* is associated with the presence of elevated concentrations of these inflammatory mediators in the urine, and is also involved in neutrophil recruitment within the infected urinary tract.[34] P fimbriae activate epithelial cells to release cytokines and chemokines by using the Toll-like receptor 4 pathway for signal transduction.[35] IL-8, also designated CXC chemokine, recruits neutrophils and other inflammatory cells to migrate to the site of infection in the urinary tract.[36] IL-8 orchestrates neutrophil recruitment by binding to two high-affinity IL-8 receptors, CXCR1 and CXCR2, expressed on the surface of uroepithelial cells. Expression of these receptors increases with infection, leading to higher IL-8 binding and greater neutrophil migration across infected epithelial cells. Neutrophils exit the blood vessels, cross the lamina propria and the epithelial barrier, and enter the urinary lumen, resulting in pyuria (Figure 36.1).[37] In experimental models, antibody to IL-8 or to the CXCR1 receptor, but not to the CXCR2 receptor, reduced neutrophil migration across cell layers, indicating that the CXCR1 receptor plays a key role in this process.[38,39] Bacterial endotoxins also facilitate chemotaxis by activating complement.

The neutrophils recruited by the cytokines kill bacteria and help clear the infection. Chemokine receptor expression was studied by Frendeus and colleagues in a group of 12 children with a history of acute pyelonephritis and recurrent UTIs and a group of 12 control children with no documented history of UTI.[40] Cell surface CXCRI expression and CXCRI-specific mRNA were low in the neutrophils of children with recurrent UTI, compared with those of matched controls. These results suggest that molecular factors in the host may contribute to susceptibility to acute pyelonephritis.

Host response and renal scarring

Renal parenchymal scarring as a result of acute pyelonephritis is intimately related to the host response to infection. Intravesical inoculation of *E. coli* in IL-8 receptor knockout (KO) mice triggered a chemokine response and neutrophil recruitment, but the neutrophils accumulated under the epithelium, and failed to cross the mucosal barrier and kill bacteria. Whereas control mice successfully cleared the infection, the KO mice developed swollen kidneys, neutrophil abscesses, and subsequent renal scarring.[41] This animal model underscores the importance of chemokine receptors in the host's ability to successfully clear infection, and suggests a potential molecular basis for the progression of acute pyelonephritis to renal scarring.

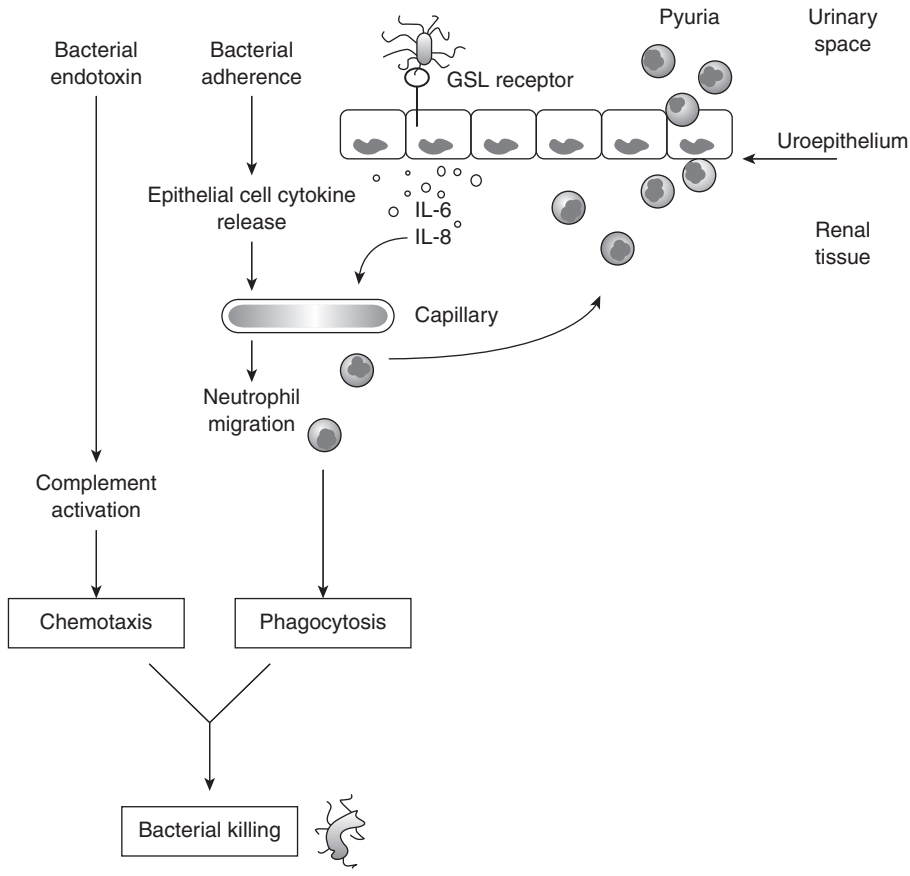

Figure 36.1 Host response to urinary tract infection. GSL, glycosphingolipid.

Susceptibility of children to urinary tract infection

Some children are prone to developing UTI and may have frequent recurrences. Several anatomic, functional, and behavioral factors can render children prone to UTI. Whereas a solitary factors may render many children susceptible to UTI, multiple risk factors may be operative in other children.

Urinary anatomy

Because of the known predisposition of females to UTI, a short urethra in girls, in comparison with boys, has long been proposed as being a factor in facilitating spread of ascending infection. Although intuitively plausible, published evidence for this hypothesis is almost nonexistent. A small urethral diameter in girls has also been cited as a reason for susceptibility of some girls to UTI. The works of Graham et al[42] and Immergut and Wahman[43] have, however, convincingly shown that the internal urethral diameter does not differ significantly between the bacteriuric and non-bacteriuric girls. In conclusion, although commonly cited, the role of normal urethral anatomy in facilitating movement of bacteria upstream into the urinary bladder is largely unclear.

Prepuce and circumcision

Circumcision is practiced as a religious and sociocultural ritual in many parts of the world. In the religious context, circumcision is widely practiced in the Jewish and Muslim faiths. Incidence of circumcision in the United States peaked at 85% in 1965.[44] Current data suggest that approximately 65% of newborns undergo neonatal circumcision in the United States.[45] The rate of circumcision in African-American neonates used to be 10–15% lower than Caucasian neonates, but recent data suggest that the circumcision rate is similar in the two races.[44,45] The circumcision rate in countries outside the United States is low. In Europe, circumcision is generally practiced for medical reasons only, and rates vary from 2% in Denmark to about 3.8% in the United Kingdom.[46,47]

The role of circumcision in preventing UTI has been recognized since the 1980s. Ginsberg et al noted that 75% of boys with febrile UTI in the first 8 weeks of life were non-circumcised.[9] In a retrospective analysis of 5261 infants < 1 year of age, Wiswell et al showed that 0.78% of these had confirmed UTI.[48] In this cohort, the incidence of UTI in females and circumcised males was 0.47% and 0.21%, respectively. In contrast, 4.21% of uncircumcised males had a confirmed UTI. These authors subsequently expanded their studies to suggest a 20- to 29-fold increase in febrile UTI in uncircumcised males in comparison

to circumcised infants.[48–51] Schoen et al also reviewed the incidence of UTI in 28 812 neonates in the Kaiser Permanente system in California. The incidence of UTI during the first year of life in the non-circumcised infants group was 2.15%, compared with 0.22% in circumcised infants – a 9.1-fold increase of UTI in non-circumcised infants.[52] These and other additional data suggest that the incidence of UTI in uncircumcised infants is 3–7 times higher than in uncircumcised infants, being significantly lower than initial estimates.[10,52–54]

The mechanism by which the intact prepuce predisposes to UTI is unclear. One possible explanation is that the prepuce allows the enteropathogenic bacteria to harbor and multiply in an uncircumcised male.[55,56] Enhanced adherence capability of the uropathogenic organisms to the non-keratinized mucosa of the prepuce has also been cited as a factor that leads to a higher incidence of UTI in non-circumcised male infants.[57] A recent study suggests that colonization by highly virulent strains of *E. coli* appears to be facilitated by the presence of prepuce in young infants.[58] The molecular mechanism for this predisposition, especially in the absence of urinary tract malformations, is unclear.

Routine neonatal circumcision: AAP view

In March 1999, the American Academy of Pediatrics (AAP) issued a revised policy statement regarding neonatal circumcision.[59] While agreeing with the potential medical benefits of circumcision, including prevention of UTI in susceptible male infants, AAP believes that the number of UTIs in male infants that can be prevented by routine circumcision does not justify advocating routine circumcision in all male newborns. The AAP reiterated its position in 2000, in response to criticism by advocates of routine circumcision.[60,61]

Voiding dysfunctions

A voiding dysfunction is defined as an abnormal micturational pattern seen in children with a normal urinary tract anatomy and intact neurogenic control of the urinary tract. The association of voiding dysfunctions and UTI is well known.[5,62–66] Patients with voiding dysfunctions have also been independently noted to have a high incidence of VUR.[63,64] Predisposition to UTI in these patients is felt to be due to incomplete bladder emptying, leading to accumulation and proliferation of uropathogenic bacteria in the bladder. Some recent studies have questioned the role of dysfunctional voiding in increasing susceptibility to UTI.[67]

Patients with voiding dysfunction may present with symptoms that the parents recognize as frequency, urgency, cross-legged posturing ('pee-pee dance'), and wetting of underpants. Other children may be infrequent voiders, with what is sometimes referred to as 'lazy bladder syndrome'. These patients are generally constipated and often remain busy with playful activities that they enjoy, thus avoiding the urge to urinate. Diagnosis of voiding dysfunction is made by a careful clinical history and a nearly normal clinical examination.

Urinary obstruction

In an unselected childhood population with UTI, the incidence of urinary obstruction has been reported to be as high as 10%.[3] In the more recent literature, however, urinary obstruction accounts for less than 1% of children with UTI caused by *E. coli*.[7,68] On the other hand, urinary obstruction is more commonly (15%) seen in children with UTI caused by *Proteus*, *Enterococcal*, *Klebsiella*, or coagulase-negative *Staphylococcal* infections.[68] In the era of prenatal ultrasound evaluation, most patients with obstructed urinary tracts are detected early, even before the onset of the first UTI. Indeed, children with posterior urethral valves may first come to medical attention because of febrile UTI, or urosepsis. Obstruction at the ureteropelvic junction, or along the ureteric length can also lead to a predisposition to UTI.

Vesicoureteral reflux

Retrograde flow of the urine from the urinary bladder into the ureters is prevented during micturition by a functional valve mechanism at the level of the ureterovesical junction (UVJ). Incompetence of the UVJ valve leads to flow of urine upstream into the ureter and the kidney, a condition known as vesicoureteral reflux or VUR. The association of VUR and predisposition to UTI is well established.

Functional anatomy

The UVJ lacks a traditionally defined valve to prevent retrograde flow of urine from the bladder into the ureter. The antireflux mechanism operative at this location is dependent on the unique anatomic configuration of the ureteral insertion into the bladder (Figure 36.2).

The ureter normally enters the bladder in an oblique fashion and traverses through the bladder muscle wall (intramural ureter) and the submucosal space (submucosal ureter), before opening at the posterolateral aspect of the base of the bladder trigone. The submucosal ureter runs a relatively long course. The ratio of intramural to submucosal ureteral length is 1:5 in a non-refluxing ureter.[69] The submucosal ureter is pliable and rests between the bladder mucosa and the bladder muscle (detrusor). As the bladder distends with urine, it leads to compression of the submucosal ureteral lumen between the mucosa and the detrusor muscle.[70,71] This anatomic arrangement creates a mechanism that prevents reflux of urine into the bladder. Integrity of this valve mechanism requires:

- an oblique intramural course of the ureter
- maintenance of an appropriate ratio between intramural and submucosal ureteral lengths (1:5)
- the location and size of the ureteral opening into the bladder.

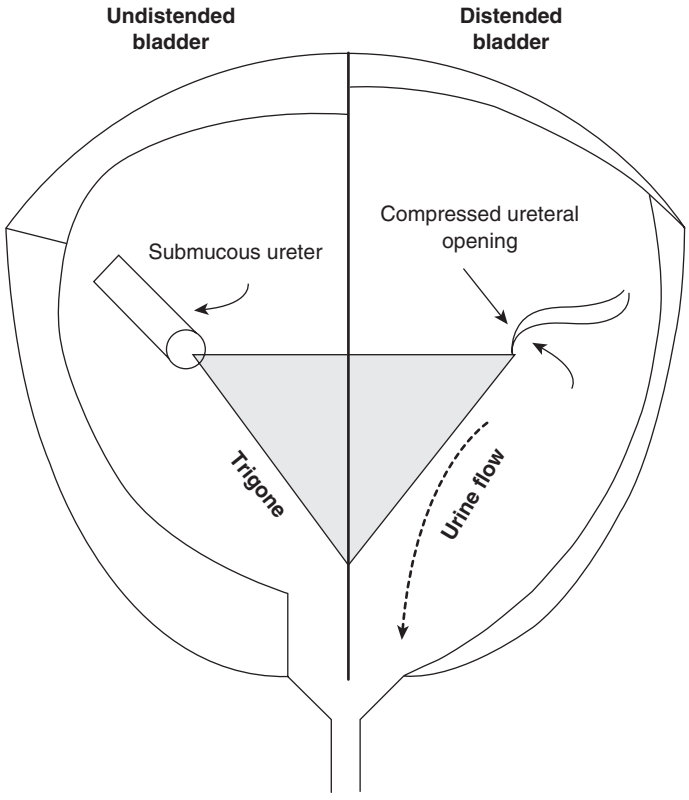

Figure 36.2 Normal anatomy of the ureteric insertion into the bladder in a distended (right side) and undistended state (left side). Compression of the intravesicular portion of the ureter and mechanism of prevention of VUR is demonstrated in the right side.

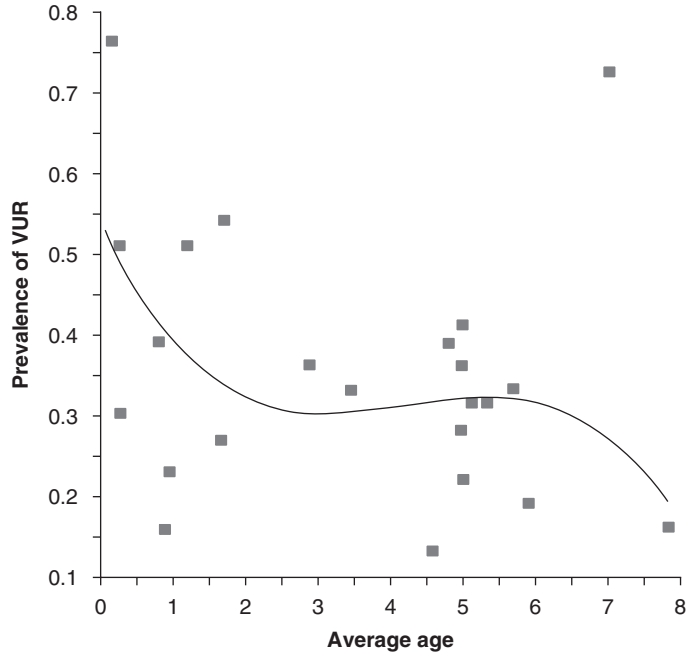

Figure 36.3 Prevalence of VUR by age. Plotted is the prevalence reported in 54 studies of urinary tract infections in children. The studies are weighted by sample size. The line is a third-order polynomial fit to the data. (Reproduced with permission from Committee on Quality Improvement Subcommittee on Urinary Tract Infection: Practice Parameter: The Diagnosis, Treatment, and Evaluation of the Initial Urinary Tract Infection in Febrile Infants and Young Children. Pediatrics, 103:843, 1999)

Prevalence

Primary VUR is the commonest congenital anomaly affecting the urinary tract. VUR has been reported in asymptomatic children without underlying urologic disorders, or a history of UTI.[72] Baily reviewed the published literature on the subject and reported the incidence of VUR to be 0.4–1.8% in children without UTI.[73] Prevalence of VUR in apparently healthy neonates has been reported to be 0.8–1.3%.[74,75] It is well known that the prevalence of VUR decreases with increasing age of children, suggesting that there is a trend towards improvement of VUR, even without any intervention throughout the childhood age spectrum (Figure 36.3).[76] Approximately 30% of older children with UTI have evidence of VUR, with a range of 20–50% in various studies.[77,78] A similarly high incidence of VUR has also been reported in neonates with UTI.[79]

The Caucasian race has a peculiarly high predisposition to VUR, whereas its prevalence is low in African-American children.[80,81] This racial predisposition for non-African-Americans has been noted in neonates as well.[82]

Familial vesicoureteral reflux

VUR can be seen in 25–50% of asymptomatic siblings of index children diagnosed as having VUR.[83–85] Children born to parents with a known history of VUR are also at a higher risk of having VUR.[86,87] Noe et al studied 36 children born to 26 parents with a known history of VUR.[86] VUR was detected in 66% of the offspring in this group. These findings suggest a familial pattern of VUR, but the mode of inheritance is unclear.

The severity of VUR seen in siblings is variable, ranging from grade I to grade IV. Most siblings and children detected as having VUR on screening are asymptomatic, but febrile UTIs are also well known to be present in others. Several studies have shown that asymptomatic VUR in siblings can be associated with renal parenchymal scarring.[88,89]

Classification of VUR

VUR in children can be classified as primary, or secondary (Table 36.1). Primary VUR is the congenital defect of the ureteral insertion into the urinary bladder that is commonly seen in children in association with UTI, or is incidentally detected in siblings of such patients. Secondary VUR is acquired in origin, and is seen less commonly in children. Table 36.2 lists the clinical conditions that are associated with a high incidence of VUR.

The gold standard for evaluation of children for VUR is contrast vesicocystourethrography (VCUG), especially in male children, but nuclear cystogram is recommended in females. These procedures are described in detail in Chapters 6 and 7. The most widely used classification of VUR is the one proposed by International Reflux Study Classification.[90]

Table 36.1 Classification of vesicoureteral reflux (VUR)

Primary
Congenital VUR resulting from malimplantation of the ureter in the bladder – associated with urinary tract infection

Secondary
Bladder outlet obstruction:
- Posterior urethral valves
- Bladder neck obstruction
- Severe urethral stricture

Neurogenic bladder:
- Spina bifida–meningomyelocele

Chronic bladder inflammation
Urinary tract infection
Traumatic:
- Following bladder surgery
- Following ureteral calculus extraction

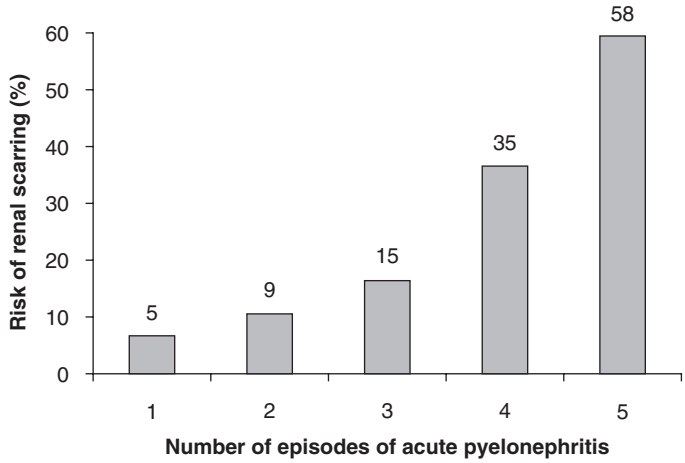

Figure 36.4 Risk of renal scarring shows a progressive increase with the number of febrile urinary tract infections in children. (Graphic representation of data from Jodal U.[91])

Table 36.2 Clinical conditions associated with a high risk for vesicoureteral reflux (VUR)

1. Prenatal detection of hydronephrosis
2. Febrile urinary tract infection
3. Siblings of index patients with VUR
4. Children of parents or close relatives with history of VUR
5. Children with voiding dysfunction
6. Children with high-grade urinary obstruction – including Hinman syndrome
7. Maticystic dysplastic kidney–contralateral ureter

Renal scarring and VUR

VUR is well recognized to be associated with renal scar formation. In general, the incidence and severity of renal scars associated with VUR increase with the grade of VUR.[91] The incidence of renal parenchymal scars is also higher in those with recurrent febrile UTIs (Figure 36.4).[91] Such renal scars were termed 'chronic atrophic pyelonephritis' in the literature predating the 1970s. Baily introduced the now-accepted term 'reflux nephropathy' as a designation for renal scars associated with VUR and pyelonephritis.[92]

The mechanism by which VUR leads to renal scarring has been a matter of considerable debate. Based on the experimental data of VUR induced in pigs by bladder outlet obstruction, Hodson et al suggested that passage of sterile urine into the renal tubules (intrarenal reflux) associated with high-pressure VUR led to renal scar formation.[93] Intrarenal reflux may be facilitated by the type of papillae in the kidney.[94] Simple papillae are those that have a convex contour, with collecting ducts opening along the convex surface. The slit-like opening of the collecting ducts is closed as the intrapelvic pressure rises, thus preventing reflux of urine into the collecting ducts. In contrast, compound papillae are larger in size and are believed to develop from fusion of two or more simple papillae. These papillae have a concave surface into which the collecting ducts open. As the intrapelvic pressure rises, the wide-open collecting ducts allow the passage of urine into the tubules. Compound papillae are often found in the polar regions of the kidney. This is believed to be the reason for the polar location of renal scars seen in association with VUR.

Other experimental data suggest that sterile VUR, by itself, is unable to result in renal scarring, and that infection plays an essential role in the development of these scars.[95,96] This is the generally held view at present. Two clinical observations strengthen this argument. First, intrarenal reflux is uncommon in children with primary VUR and can be demonstrated at most in only 5–15% of children with primary VUR.[97,98] Secondly, preventing UTIs in children with antibiotic prophylaxis, despite continued VUR, reduces the incidence and severity of renal scars associated with primary VUR.[99,100]

Blood groups

In addition to underlying structural urogenital anomalies, an individual's blood group may also influence predisposition to UTI.[101–104] Blood group antigens are genetically determined carbohydrate moieties present on erythrocytes and epithelial cells, including uroepithelial cells. Blood group antigens may influence the binding of fimbriated bacteria to carbohydrate receptors present on uroepithelial cell surfaces by producing a specific receptor site for bacteria, or by blocking an exposed receptor site. Women with recurrent UTIs have an increased frequency of Lewis blood group non-secretor and recessive phenotypes.[102] Jantausch et al reported that the relative risk for UTI was 3.2 in children with the Lewis (Le) (a-b-)

phenotype.[103] Sheinfeld et al found that children with genitourinary structural anomalies, whose uroepithelium reflected a non-secretor phenotype, had a history of UTI.[104] These children had low or undetectable levels of ABO and Le^b reactivity in their uroepithelium compared with children without a history of UTI, whose uroepithelium demonstrated strong ABO and/or Le^b immunoreactivity. In contrast, Albarus et al[105] found no association between blood groups and susceptibility to UTI in 65 children with acute febrile UTI and control children. Identification of children at risk for UTI by specific blood group phenotypes needs further investigations, and may prove to be a useful tool in prevention of UTI and its sequelae.

Clinical manifestations

Manifestations of UTI vary with age, site of infection within the urinary tract, and the severity of infection. From a clinical perspective, infection of the urinary tract may be discussed either as a non-febrile UTI (acute cystitis) or as a febrile UTI (acute pyelonephritis).

Non-febrile UTI (cystitis)

Among preschoolers, cystitis is more commonly seen in girls than in boys. Of the 157 children <6 years old identified with first-time symptomatic non-febrile UTI by Marild and Jodal, 130 were girls and only 27 were boys.[5] The peak incidence of non-febrile UTI in preschool girls in this study was 9.4 cases/1000 at-risk children, and occurred in the 3rd year of life. Thereafter, the incidence gradually declined to a stable level of 2.5 cases/1000 at-risk children. In contrast, the peak incidence of non-febrile UTI in preschool boys in this study was only 2.8/1000 at-risk children, and was noted during the 1st year of life.[5]

In children who can verbalize (usually >3–4 years of age), dysuria and suprapubic pain are common manifestations of cystitis. Symptoms of dysuria may be difficult to ascertain in younger children. In 49 boys between 6 and 12 years of age with bacteriologically proven UTI, Hallett et al found dysuria or frequency (in 82%), enuresis (in 66%), and abdominal pain (in 39%) as the most common symptoms.[106] Urinary incontinence is another common symptom of cystitis, especially in girls. In a prospective study of 251 girls between 4 and 14 years of age with recurrent UTI, Sørensen et al studied the association of diurnal incontinence with UTI. During a follow-up of 6–12 months, 110 girls (44%) were noted to have urinary incontinence in association with the onset of UTI.[107] Parental observations range from a general reluctance of the child to urinate, to excessive crying and abdominal pain. Parents often report the urine to be foul smelling. But these symptoms may be subjective and cannot be relied on.

Gross hematuria has been reported to be a common manifestation of bacterial cystitis in children. Bergstrom et al noted macroscopic hematuria as a clinical symptom in 26% of patients with UTI (both males and females), ranging in age from 1 to 16 years.[6] Hematuria was more common in males (43%) than in females (9%) in this study. In another study, Ingelfinger et al reported that of the 158 children with macroscopic hematuria seen in the emergency room, UTI was the underlying etiology in 26% of cases.[108] Cystitis has been reported in children who self-inject or manipulate the urethra.[109] Hematuria is also a common manifestation (60%) in such children.

Febrile UTI (acute pyelonephritis)

Association of fever in a patient with a positive urinary culture presumptively suggests renal parenchymal infection or acute pyelonephritis. Other symptoms of acute pyelonephritis include abdominal pain, and costovertebral angle pain and tenderness, which are more commonly present in older children and adolescents. In younger children and infants, in addition to fever, other non-localizing symptoms – such as excessive crying, irritability, vomiting, feeding problems, and lethargy – are often present. Dysuria is an uncommon manifestation of febrile UTI in children <1 year of age but up to a quarter of older children may complain of this symptom.[110] Febrile UTI, or acute pyelonephritis, associated with manifestations of sepsis is often referred to as 'urosepsis', and is particularly common in children with clinically significant urinary tract anomalies such as obstructive disease or VUR.

Bacteremia is present in 4–9% of infants and young children <1 year old with UTI.[111,112] Fever may be the only symptom in many patients with UTI-associated bacteremia, especially early in their presentation. Symptoms of chills and rigors may also be seen in these patients, but clinical symptoms alone are poor indicators of bacteremia.[110] Meningitis may be present in patients with urosepsis, especially in the <3 months age group.[112]

Acute renal failure is an uncommon manifestation of acute pyelonephritis. Such patients may require dialysis therapy, and complete renal recovery after successful treatment of the infection is possible.[113]

UTI in neonates and infants

The diagnosis of UTI needs to be considered in neonates and infants <3 months of age with sepsis or unexplained fever. This is even more important in infants with known urinary tract abnormalities such as hydronephrosis, obstructive uropathy, and VUR. Fever may be absent in some patients of this age group, being particularly true of neonates. Winberg et al found fever as an accompanying symptom in only 42% of neonates with acute pyelonephritis.[3] Hypotension, shock, jaundice, failure to thrive, diarrhea, vomiting, feeding problems, irritability, cyanosis, polyuria, and metabolic acidosis have also been reported as presenting manifestations in neonates and infants <3 months of age with acute pyelonephritis.[7,114]

Diagnosis of urinary tract infection

The aims of investigations in a child with UTI are:

- to confirm the diagnosis
- to identify the infecting organism
- to localize the site of infection and identify children with acute pyelonephritis
- to recognize patients with urinary tract malformations.

An algorithm for investigations of children with UTI, based on current recommendations, is shown in Figure 36.5.

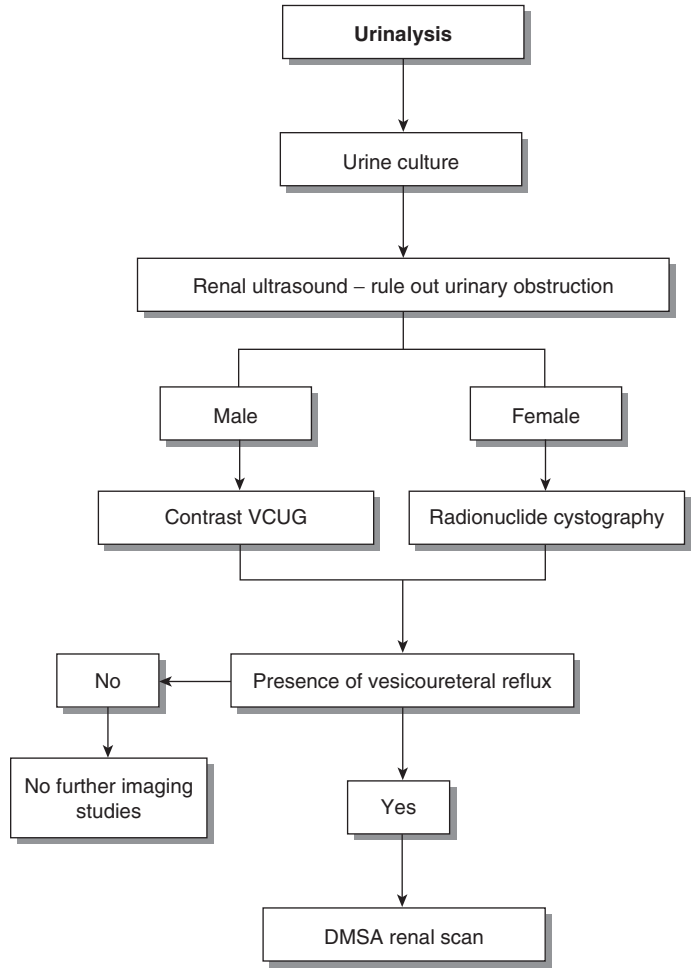

Figure 36.5 Algorithm for diagnostic evaluation of urinary tract infection in children 2 months to 2 years.

Urinalysis

Urinalysis is the initial laboratory study carried out on patients with a presumptive diagnosis of UTI, especially in the office or emergency room setting.

Urine color and smell

Turbid urine may be an indication of pyuria and UTI. Clarity of urine was shown to have a negative predictive value of 100% for absence of UTI in some reports.[115] In contrast, Bulloch et al found that 3 of the 29 children with UTI and positive urine culture were regarded as having clear urine.[116] Therefore, clarity of urine has some limitations as a discerning indicator for absence of UTI.

Parents often report an abnormal smell to be suggestive of onset of UTI in children In a study of 110 patients, 52% of parents considered that their child's urine smelled different from usual, but only 6.4% of the children had a positive urine culture.[117] These observations suggest that urine smell is also a poor indicator of screening for UTI.

Urine microscopy

Bacteriuria. Detection of any bacteria in the uncentrifuged urine slide stained with Gram stain has been used as the gold standard for presumptive diagnosis of UTI. In a meta-analysis of published studies in children, Gorelick and Shaw reported that the presence of any bacteria in the Gram-stained urine slide demonstrated a true positive rate of 0.97 (high sensitivity) and a false-positive rate of only 0.05 (high specificity).[118] The limitations of this test for a wide acceptability in clinical practice are that it is time consuming and requires expertise in reading the Gram stain and identifying of organisms in the urine sample.

Pyuria. Pyuria, or light-microscopy visualization of more than 10 white blood cells (leukocytes)/high-power field (WBCs/hpf) in centrifuged urinary sediment is considered presumptive evidence of UTI. The presence of 10 WBCs/hpf has been noted as having a true positive rate of 0.77 and a true negative rate of 0.11.[118]

Variables such as centrifuge speed, centrifugation time, volume of urine centrifuged, and the volume of urine used for resuspension can influence the quantitation of pyuria. Sterile pyuria, or urinary WBC excretion, without concurrent evidence of bacterial infection or UTI, may be seen in other clinical conditions (Table 36.3). Other limitations include neutropenia, where the patient may not be able to mount a urinary WBC response, and infection with organisms such as *Proteus* sp, which produce an alkaline urine and lead to disruption of the urinary WBCs in urine and an apparent absence of pyuria in the face of UTI.

Leukocyte esterase. Testing for leukocyte esterase may overcome some of the limitations of urinary microscopy in identifying leukocyturia. Leukocyte esterase is present in the neutrophils and can be assayed in the urine by dipstick strips. False-negative tests may be caused by the presence of ascorbic acid, high urinary protein, glycosuria, urobilinogen, gentamicin, nitrofurantoin, cephalexin, and boric acid. False-positive tests can results from the presence of imipenem and clavulanic acid in the urine.

Nitrite test. This test is based on the fact that the bacterial enzyme nitrate reductase can convert urinary nitrate to nitrite, which can be detected by several chemical methods. The nitrite test has now been incorporated in commercially available dipstick test strips.

Although a good screening test, the nitrite test cannot be relied on as a confirmatory test for UTI. Kunin et al found that the test was positive in 65.4% of patients with culture-positive UTI if performed one time.[119] The nitrite test does not identify patients with Gram-positive infections, because they lack the nitrate reductase enzyme. Also, conversion of the urinary nitrate to nitrite requires sufficient time (usually 3–4 hours in the bladder), even in the presence of Gram-negative infection. In patients with UTI and urinary frequency, the reaction time may be less than optimal, leading to poor conversion of nitrate and a falsely negative test. High urine specific gravity reduces the sensitivity of this test, and high urinary ascorbic acid may also produce a negative test in the presence of a small amount of nitrite.

Urine culture

Urine collection. Culturing urine remains the traditional gold standard for confirming the diagnosis of UTI. Potential contamination of the urine sample is a well-recognized problem that can make interpretation of the culture results difficult. Collection of urine in infants by a collection device such as a U-Bag is associated with a high rate of bacterial contamination and is not an acceptable collection method for urine culture.[120]

In order to reduce the risk of bacterial contamination, urine for culture is collected by one of following methods:

- clean catch
- catheterization
- suprapubic aspiration in neonates.

The clean catch method involves cleaning the external genitalia with a mild antiseptic and collecting urine in midstream into a sterile container. This method is generally acceptable for adolescents and cooperative children. Suprapubic urine aspiration involves percutaneous insertion of a needle into the urinary bladder and aspirating urine into a sterile syringe. This method is reserved for use in neonates and infants < 2 months of age, when the urinary bladder is a pelvic organ. The single most important factor in success of the procedure is whether or not the bladder is palpable at the time of the aspiration. The success rate can be further enhanced by the use of ultrasound guidance. Catheterization of the urethra to obtain urine is the preferred method for collection in a non-cooperative patient, in whom clean catch collection of urine is not possible. If a delay in the inoculation of the culture is expected, urine specimens should be refrigerated in order to prevent the overgrowth of bacteria at ambient temperature.

Bacterial count. A growth of $>10^5$ organisms, or colony-forming units/milliliter (CFU/ml) of a single species of bacteria in a catheterized urine sample is considered positive evidence of UTI (Table 36.4).[9] Any growth of a single organism in a sample obtained by suprapubic aspiration is regarded as a strong indication of UTI. From their study of catheterized urine cultures in patients < 24 months of age, Hoberman et al concluded that UTI was most accurately diagnosed by a colony count of 50 000 CFU/ml.[121]

Colony counts lower than the recommendations in Table 36.4 may be considered diagnostic of UTI in certain clinical circumstances. These include patients currently receiving antibiotic therapy, patients with complete ureteral obstruction preventing the flow of infected urine and bacteria into the bladder, patients with urinary frequency who may have a reduced dwell time of urine in the bladder, and patients infected with organisms (e.g. *S. saprophyticus*) that are known to have lower colony counts in urine culture.[14]

Radiologic imaging

The purpose of radiologic investigations in patients with UTI is two fold:

- to search for any malformations of the urinary tract that may predispose to UTI
- to establish the diagnosis of acute pyelonephritis, when other evidence may be lacking.

A consensus regarding the types of imaging studies necessary in patients with first UTI is still lacking.

Table 36.3 Clinical conditions that may be associated with sterile pyuria

1. Partially treated UTI
2. Interstitial nephritis
3. Renal tubular acidosis
4. Glomerulonephritis, especially acute postinfectious glomerulonephritis
5. Renal cystic diseases
6. Renal stone disease
7. Hydronephrosis
8. Appendicitis
9. Dehydration
10. Meatal or urethral irritation, especially in males
11. Vaginitis in females
12. Renal tuberculosis

Table 36.4 Microbiologic criteria for positive urine culture

Method of collection	Threshold for diagnosis of UTI
Suprapubic aspiration	1000 CFU/ml
Catheterization of bladder	50 000 CFU/ml
Midstream clean catch	100 000 CFU/ml
Bagged urine culture	Unreliable

CFU, colony-forming unit; UTI, urinary tract infection.

Ultrasound

Current recommendations of the American Academy of Pediatrics are that all children < 2 years of age with a febrile UTI undergo an upper urinary tract evaluation by ultrasound and a cystographic study after the diagnosis of first UTI.[76] Ultrasound may be the initial investigation of choice when suspicion of complications such as renal abscess or perinephric abscess is being considered in a patient with acute pyelonephritis (Figure 36.6). The role of ultrasound in the diagnostic evaluation of first febrile UTI has been contested recently. Hoberman et al reviewed the radiologic investigations of 309 children < 2 years of age and concluded that renal ultrasound provided no additional diagnostic advantage in most patients.[122] Change in therapy as a result of ultrasound findings would have been indicated in < 1% of cases. Alon and Ganapathy studied radiologic imaging in 124 children with first febrile UTI.[123] Ultrasound detected only 1 patient with urologic abnormality. Similarly, Zamir et al evaluated the role of ultrasound in 255 children (0–5 years of age) hospitalized with first febrile UTI. They were able to detect only 4 cases of renal and urinary tract abnormality;[124] these ultrasound findings did not influence therapy or follow-up in any patient. In contrast, Giorgi et al were able to find significant urinary tract abnormalities that altered their treatment plan in 9 (4.4%) of 203 patients (0–2 years of age).[125] In summary, the role of ultrasound as a part of recommended radiologic investigations of first UTI is undergoing rethinking, and is likely to change.

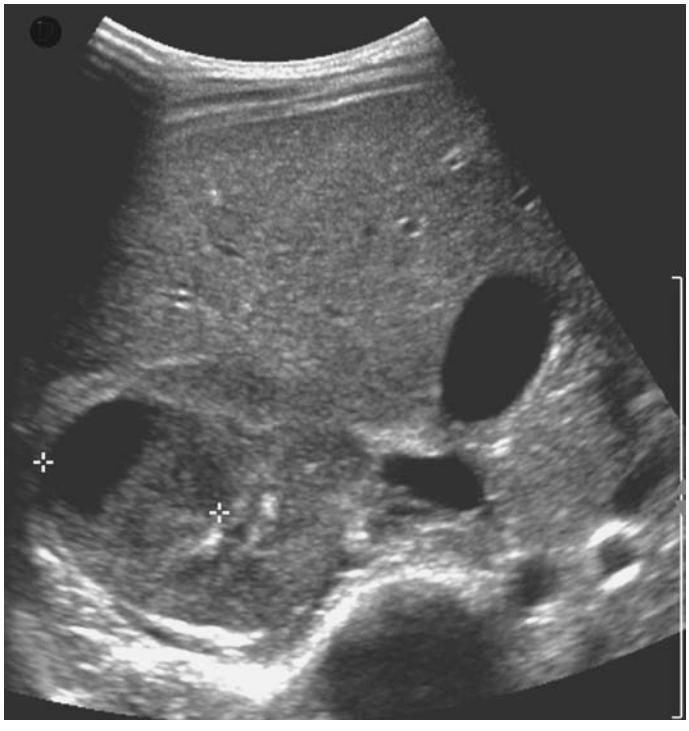

Figure 36.6 Ultrasound of the kidney showing an intrarenal abscess. The abscess shows mixed fluid and solid consistency. Aspirated fluid from the abscess grew *E. coli*.

Vesicocystourethrography and radionuclide cystography

Patients with febrile UTI should undergo investigations to rule out the possibility of VUR. This can be done by either VCUG or radionuclide cystography (RNC). Contrast VCUG with fluoroscopic guidance is recommended in male children with UTI, so that the anatomy of the bladder and urethra can be well defined. RNC is an acceptable alternative to contrast VCUG, particularly in females, where bladder outlet and urethral obstructive lesions are unlikely. The advantage of a nuclear cystogram is that it exposes children to only approximately 1–2% of the radiation dose used in contrast fluoroscopy VCUG.

Timing of VCUG or RNC in a patient with a newly diagnosed febrile UTI has been undergoing rethinking. So as not to overdiagnose transient VUR associated with UTI, the general recommendations in the past have been to defer VCUG/RNC for 4–6 weeks after the diagnosis of UTI. In several recent studies, however, it has been shown that the incidence of VUR within 1 week of diagnosis of UTI is not different from cystograms done later (1–4 weeks).[126,127] It is imperative that patients are on appropriate antibiotic therapy if the test is undertaken early, and are on suitable prophylaxis for prevention of UTI if the test is deferred for 4–6 weeks. Prophylactic antibiotics can be discontinued after the diagnosis of VUR is ruled out.

DMSA renal scan

Intravenous pyelography (IVP) has, in the past, been used as the gold standard for detection of pyelonephritic scars following acute pyelonephritis. In the last two decades, a radionuclide scan, using technetium-99m-dimercaptosuccinic acid (DMSA) has evolved as an attractive alternative to IVP for evaluation of pyelonephritic renal scars or reflux nephropathy. Furthermore, a DMSA renal scan done early in the course of a febrile UTI can also help in the diagnosis of acute pyelonephritis, in cases where other evidence may be lacking.[128,129] DMSA renal scanning is further discussed in Chapter 7.

Preference for diagnostic use of the DMSA renal scan in the investigation of febrile UTI is highly institution-dependent. The American Academy of Pediatrics Subcommittee on Urinary Tract Infection has not recommended a DMSA scan as a required imaging investigation of children < 2 years of age.[76] Others, in contrast, have advocated replacing cystograms with DMSA renal scans as the initial investigation in children with UTI.[130] The utility of this approach and its limitations in clinical circumstances need to be further investigated.

Recurrent urinary tract infection

After the first episode of UTI, recurrent UTI may be seen in 30–40% of patients, especially in those with anatomic urinary tract anomalies such as VUR, urinary obstruction, or bladder diverticulum.[131–135] Female sex, dysfunctional voiding, and bladder instability, are other risk factors for recurrent UTIs.

Treatment of urinary tract infection

The aims of antimicrobial treatment for urinary tract infection are:

- to clear the acute infection
- to prevent urosepsis
- to reduce the likelihood of renal damage.

The principles for selection of antibiotic therapy for UTI are similar to the guidelines used in choosing antibiotics for other serious infections, which are that the bacteria are susceptible, and the antibiotic is well-tolerated by patients, has a low-toxicity profile, and is cost-effective.

Initial empiric therapy

Initial antibiotic therapy of UTI is often empiric. The susceptibility pattern of the infecting organism grown in urine culture should be used subsequently to guide transition to an appropriate antimicrobial agent. The choice of empiric antibiotics is dictated by the sensitivity pattern of the organisms in the community, especially in view of increasing resistance of uropathogens to antimicrobial agents over the last two decades.[136] Up to 40–53% of uropathogens are known to be resistant to ampicillin or amoxicillin, and 5% are resistant to trimethoprim–sulfamethoxazole.[137,138]

Trimethoprim–sulfamethoxazole, second- and third-generation cephalosporins, and Augmentin (amoxicillin–clavulanate) are generally used as the initial empiric therapy for the treatment of UTI in the United States.[139] Table 36.5 details the dosing regimens for commonly used antibiotics to treat UTI. Antibiotics given to children should not exceed the maximum daily adult dosage.

Febrile UTI

First three months

Neonates (<1 month of age) with febrile UTI should be hospitalized and treated with intravenous therapy throughout their entire antibiotic treatment course. Bacteremia and meningitis

Table 36.5 Antibiotic treatment for common urinary pathogens

Organism	Oral antibiotic therapy	Intravenous antibiotic therapy
Gram-negative bacteria		
Enterobacteriaceae	Amoxicillin: 40 mg/kg/day divided q 8–12 h Amoxicillin–clavulanate: 45 mg/kg/day divided q 12 h Cephalexin: 50 mg/kg/day divided q 6–8 h Cefprozil: 30 mg/kg/day divided q 12 h Cefuroxime axetil: 30 mg/kg/day divided q 12 h Cefixime: 8 mg/kg/day once daily TMP–SMZ: 8–12 mg TMP/kg/day divided q 12 h	Cefazolin: 50 mg/kg/day divided q 8 h Cefuroxime: 150 mg/kg/day divided q 8 h Cefotaxime: 150 mg/kg/day divided q 8 h Ceftriaxone: 50–75 mg/kg/day q 24 h Gentamicin: 6 mg/kg/day divided q 8 h in children, 7.5 mg/kg/day divided q 8 h in neonates
Pseudomonas aeruginosa	Quinolone antibiotics are effective against *P. aeruginosa* but are not approved for use in children <18 years of age	Ceftazidime: 150 mg/kg/day divided q 8 h or Timentin: 200 mg/kg/day divided q 6 h plus an aminoglycoside
Gram-positive bacteria		
Enterococcus	Ampicillin: 200 mg/kg/day divided q 6 h	Ampicillin: 200 mg/kg/day divided q 6 h or Vancomycin: 40 mg/kg/day divided q 6–8 h plus gentamicin in a neonate or immuno-compromised patient
Group B streptococcus	Penicillin G: 150 000–200 000 units/kg/day divided q 6 h or Ampicillin: 200 mg/kg/day divided q 6 h	Ampicillin: 200 mg/kg/day divided q 6 h
Staphylococcus aureus	Cephalexin: 50 mg/kg/day divided q 6–8 h if organism is susceptible	Oxacillin 100 mg/kg/day divided q 6 h or Cefazolin: 50 mg/kg/day divided q 8 h if susceptible, or Vancomycin: 40 mg/kg/day divided q 6–8 h
Staphylococcus saprophyticus	TMP–SMZ: 8–12 mg/kg TMP/day divided q 12 h if susceptible. Use susceptibility results to guide therapy	Use susceptibility results to guide therapy

should be excluded by obtaining blood for culture and examining and culturing the cerebrospinal fluid. Inpatient intravenous antibiotic therapy is recommended due to the inability of young infants to adequately absorb oral antibiotics and the immaturity of the young infant's immune system, and consequent increased risk for disseminated infection.

Some clinicians, including these authors, recommend initial parenteral therapy for all infants up to 3 months of age with UTI, especially if they are ill-appearing.[140] Parenteral therapy should continue until the infants improve clinically (usually 3–7 days). Thereafter, oral antibiotic therapy is continued to complete a total of 14 days of antibiotic therapy. Empiric parenteral antibiotic therapy for infants < 3 months of age can consist of the combination of ampicillin and gentamicin, which provides coverage for *Group B Streptococcus* and *Enterococcus*, and Gram-negative organisms. Alternatively, cefotaxime alone, or the combination of cefotaxime and gentamicin can be considered.[140]

Outpatient management may be considered in carefully selected 1–3-month-old infants with febrile UTI, provided they do not appear acutely ill, do not have bacteremia or meningitis, and are able to be followed closely.[137,140] Outpatient treatment with ceftriaxone or gentamicin given every 24 hours can also be an acceptable alternative in such patients. Parenteral therapy should be continued until the infant is afebrile for 24 hours, with the remainder of the 14-day total course of therapy completed with oral antibiotics.

3–24 months

Oral cefixime may be an option to treat 3–24-month-old infants with febrile UTI. The effectiveness of oral antibiotic therapy in treating febrile UTI in children 1–24 months has been established in a multicenter randomized clinical trial of 306 children.[137] Patients were assigned to receive either oral cefixime for 14 days (double dose on the first day) or intravenous cefotaxime for 3 days, followed by oral cefixime for 11 days. Urine culture became sterile in all patients after 24 hours of treatment. Time to defervescence of fever was 25 hours in the oral therapy group, compared with 24 hours for children who received initial intravenous therapy.

Older children and adolescents

Oral cefixime can also be used to treat older children and adolescents with febrile UTI. Alternately, a short course of intravenous antibiotic therapy (2–4 days), followed by oral antibiotic therapy, may be used. In children treated with intravenous antibiotics, single daily dosing of aminoglycosides is reported to be as safe and effective as every 8-hour dosing.[141] Patients with acute pyelonephritis are usually treated with antibiotics for 14 days.[76,137] Studies comparing 10 days of antibiotic treatment with 14-day treatment regimens have not been done so far.

Cystitis

Oral antibiotic treatment is generally adequate for treatment of uncomplicated cystitis. A short course of antibiotics (3 days) has been shown to be effective for treatment of adults with uncomplicated cystitis and normal urinary tract anatomy. A short course of oral antibiotics has also been shown to be safe and effective in treating cystitis in children with normal urinary tracts.[142] In these studies, there were no significant differences in recurrence of UTI, or development of resistant organisms, at the end of treatment with short-course antibiotic therapy.

Single-dose antibiotic therapy is inadequate for the treatment of cystitis in children.[142,143] Madrigal et al noted an unacceptably high recurrence rate of UTI (20.5%) in children treated with a single dose of trimethoprim–sulfamethoxazole, compared with a recurrence rate of 5.6% and 8%, for children treated with a 3-day and 7-day course of treatment with trimethoprim–sulfamethoxazole, respectively.[144]

Treatment of vesicoureteral reflux

Early literature on treatment of VUR suggests a strong bias towards surgical correction of this congenital disorder, especially because of the ability of surgery to definitively correct the abnormality in 95–98% of cases.[145,146] But, as more information about the natural history of VUR has evolved, opinion regarding the role of surgery in the management of VUR in children has also shifted. From the published data it is clear that the prevalence of VUR decreases with age and that there is a spontaneous resolution of reflux in approximately 50–60% of children followed for at least 2 years, especially in those with grade III or less VUR (Figure 36.7)[147,148] These observations have laid the foundation for a non-surgical approach to the management of VUR.

The Birmingham Reflux Study Group performed a prospective trial of operative and non-operative treatment of VUR in 161 children.[145] Patients were followed for up to 5 years. Surgical treatment resolved VUR in 98% patients. On the other hand, VUR persisted at 5 years in 57% of ureters when treated non-operatively. Recurrence of UTI was, however, comparable in two groups, being 22% in the operative group and

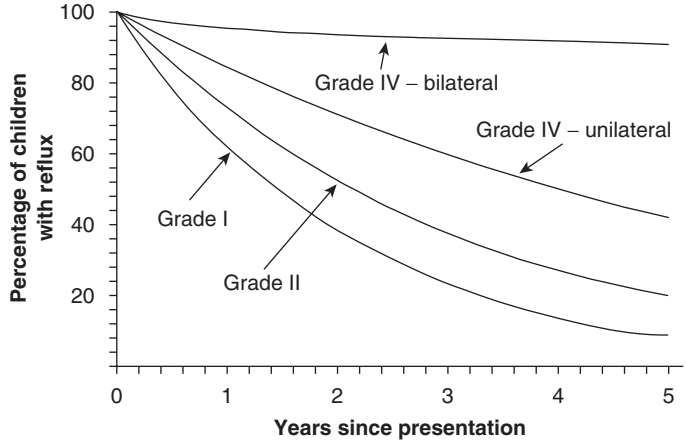

Figure 36.7 Percent chance of reflux persistence for 1–5 years following presentation. (Reproduced with permission from J Urol, 157: 1846–1851, 1997.)

29% in the medical therapy group. The authors concluded that there was no superiority of surgical treatment over medical management of VUR in children.

In 1980, the International Reflux Study Group in Children initiated a prospective, randomized study of medical and surgical therapy. The study determined that in the 5 years of the trial, there was no difference in the frequency of UTI or renal scarring in the groups that underwent medical or surgical therapy.[149] Skoog et al studied 545 children with VUR in 844 ureters, over a period of 10 years.[147] Their approach consisted of long-term antibiotic prophylaxis for prevention of UTI. In 36% of patients (39% ureters), the VUR resolved spontaneously. Mean duration of reflux in those with spontaneous resolution was 1.69 years, with a resolution rate of 30–35% each year. The severity of VUR affected the rate of resolution: grade I VUR resolved quicker (1.56 years) than grade III VUR (1.97 years).

In a meta-analysis of the published randomized controlled trials of interventions in VUR, antibiotics alone and surgery with antibiotic prophylaxis (combined group) were compared for recurrence of UTI and radiologically documented renal growth and parenchymal scarring.[150] By 2 years, the frequency of UTI in the antibiotic-only group varied from 0 to 42%, and was between 20 and 22% in the combined group. There was no difference in renal growth, new scar formation, and progressive renal parenchymal defects in the two groups. The American Urologic Association Pediatric Vesicoureteral Reflux Guidelines Panel noted the risk of acute pyelonephritis in antibiotic treatment groups to be 2.5 times higher than in those treated by surgery.[151] Although the lack of benefit of surgical intervention for most patients is clear, some have questioned whether any intervention, including prophylactic antibiotics, is able to prevent the sequelae of primary VUR.[150,152]

Initial treatment for all patients with VUR consists of antibiotic prophylaxis. Based on available scientific evidence, prophylactic antibiotics are used continuously.[151,152] Controlled trials of intermittent antibiotic treatment for VUR have not yet been undertaken. Surgical correction is recommended for patients with grade V VUR, patients with progression of renal scarring while on antibiotic prophylaxis, patients with progression of VUR grade, and for the non-compliant patient.[151,152] Girls with grade III or higher may be considered for an early surgical approach because of a higher risk of recurrent pyelonephritis.[151]

Endoscopic injection of bulking agents in the subureteral space has been suggested as a treatment modality for VUR.[153] Dextranomer–hyaluronic acid copolymer (Deflux), one such bulking agent, was approved by the US Food and Drug Administration (FDA) for clinical use. The cure rate of VUR with this procedure is approximately 60–70% with first treatment.[154] More than one treatment may be necessary for 'cure' of VUR in some patients. The indications for endoscopic injection (sting) of ureteral bulking are unclear at present. The procedure may be offered to children with grade II to grade IV VUR whose parents are unwilling to continue long-term antibiotic therapy. Whether or not the endoscopic procedure will prevent renal scarring and recurrent UTI has not been assessed yet.

Prophylactic antibiotic therapy

Use of long-term prophylactic antibiotic therapy (defined as more than 2 months of use) for prevention of UTIs in patients with VUR is well accepted. Prophylactic antibiotics are also used in patients with first-documented UTI who are awaiting imaging studies. The rationale for use of prophylactic therapy is to avoid the morbidity associated with acute pyelonephritis and to prevent renal scarring. Disadvantages of prophylactic antibiotic therapy are the side effects associated with the antimicrobial agent, the potential for development of resistant organisms in the host, and the consequences of antibiotic usage on the community.

Nitrofurantoin (2 mg/kg/day), or trimethoprim–sulfamethoxazole (trimethoprim dose 2 mg/kg/day), prescribed as a single nightly dose, are the two commonly used antimicrobial agents for prevention of UTI (uroprophylaxis). Nitrofurantoin has been found to be more effective in prevention of recurrence of UTI, as compared with trimethoprim–sulfamethoxazole.[155] However, patients taking nitrofurantoin have a higher rate of discontinuation of therapy due to side effects, primarily affecting the gastrointestinal tract, compared with trimethoprim. In patients with VUR, the same dose of the above drugs may be continued until the reflux completely resolves. Antibiotic therapy needs to be combined with frequent emptying of the bladder, avoiding constipation, and practicing good urogenital hygiene.

In the neonates and infants up to 2 months of age, ampicillin (dose 20 mg/kg/day) is generally the preferred drug for uroprophylaxis. Trimethoprim–sulfamethoxazole should be avoided until completion of the second month of life.

There is no clear consensus about the need or efficacy of prophylactic antibiotics in treating patients with recurrent UTIs and a radiologically normal urinary tract. Williams et al reviewed the clinical trials comparing prophylactic antibiotic therapy with no treatment or placebo in children for prevention of recurrent UTI.[134] In children with normal urinary tract anatomy, the duration of antibiotic treatment ranged from 10 weeks to 12 months. The recurrence rate for UTI for children in the placebo group was 63%, and there was a significant reduction of risk of recurrent UTI in all of the trials reviewed.

Complications of urinary tract infection

Renal scars

Acute pyelonephritis has the potential to cause tubulointerstitial damage and renal scar formation. Host response, tubular injury, and ischemia during acute pyelonephritis result in the formation of renal parenchymal scars. Using DMSA renal scan, renal parenchymal abnormalities can be detected in 50–85% of children with a first episode of acute pyelonephritis.[156,157] Residual changes of chronic parenchymal scarring occur in approximately 60% of patients with initial radiographic

abnormalities in the DMSA scan and complete resolution of DMSA abnormalities is seen in the remaining 40% of cases.[156] The incidence of chronic renal scars in children investigated for febrile UTI is variable and has been reported in 8–63% of patients, often in association with recurrent UTIs and structural urinary abnormalities.[3,158,159] Risk factors associated with renal scarring in acute pyelonephritis are listed in Table 36.6.

Severity of VUR influences renal scarring, being more common in grade III or higher.[91] The number of acute pyelonephritis events also has a bearing on the incidence of renal scarring. Jodal reported that renal scars were seen in only 9% of children with one episode of acute pyelonephritis, whereas 58% of children with four or more episodes of pyelonephritis developed chronic scars.[91] Pyelonephritic renal scars are usually present in the upper and lower poles of the kidney, possibly because of the type of papillae present in these regions. Once scars are formed, they do not regress. Indeed, renal tissue in the area of scars may demonstrate progressive volume loss. Early and effective treatment of acute pyelonephritis prevents renal parenchymal damage and may hold an important key to preventing renal parenchymal injury and scar formation.[160]

Renal scars may be seen in approximately 10% of children who are investigated for first UTI.[3,158] Such scars are sometimes denoted as 'primary scars', which are more common in boys. Girls, on the other hand, are more prone to developing recurrent UTI and 'secondary renal scars'.

Hypertension

Hypertension can result from renal scar formation in patients who have had acute pyelonephritis, often in association with VUR or another urinary tract anomaly. The incidence of hypertension in patients with VUR and renal scarring has been reported to be 6–23%.[151,161–164] Hypertension can also be seen in children with a history of UTI without any evidence of renal parenchymal scars. However, renal scarring (in VUR) increases the relative risk of hypertension 2.9 times, as compared with those without renal scarring.[151] Abnormal blood pressure readings in ambulatory blood pressure records of adults with a history of UTIs in childhood have been documented in 9% of patients with renal scars and in 6% of patients without documented scars.[161]

Table 36.6 Factors associated with increased risk for renal parenchymal scarring following acute pyelonephritis

1. Urinary tract abnormalities:
   - Vesicoureteral reflux
   - Urinary obstruction
   - Duplicated collecting system
2. Delay in treatment of acute pyelonephritis >48 hours
3. Recurrent acute pyelonephritis

Chronic kidney disease

Although impaired renal function and chronic kidney disease (CKD) are well reported in patients with VUR and other causes of renal scarring, their precise prevalence is unclear. The United Network of Organ Sharing (UNOS) lists tubulointerstitial diseases as the etiology of end-stage renal disease (ESRD) in 4.3–8.7% of the children and adolescents undergoing renal transplantation.[165] Although many of these children have reflux nephropathy or recurrent UTIs, separating these patients from this grouping is nearly impossible. Of the 7939 children and adolescents in the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database, reflux nephropathy has been reported as the diagnosis of ESRD in 409 (5.1%) of cases.[166] Martinell et al followed 111 girls with UTI for a median of 15 years after their first documented UTI:[167] 54 of these patients had renal scars; the incidence of CKD was 6.3% in all patients, and 12.9% in those with renal scars. Similarly, Smellie et al followed 226 children with VUR and UTI into adulthood over 10–41 years.[168] CKD developed in 10% of adults in whom renal function assessed, and ESRD evolved in 1.9%. Interestingly, Sreenarasimhaiah and Hellerstein have argued that urinary tract infections are an uncommon cause of ESRD in children. They were unable to find any patient in their unit to be in the ESRD program over 10 years of review.[169]

Fungal urinary tract infection

Fungal UTIs in children are primarily caused by *Candida* species, and are most frequently seen in neonates or older children in an intensive care unit, in immunocompromised patients, and in those with prolonged indwelling urinary catheter drainage. Bryant et al reported a prevalence of 0.5% candiduria among 8790 infants admitted to the neonatal intensive care unit.[170] *Candida* species was the pathogen recovered in 42% of neonates with hospital-acquired UTI.[171]

Candida UTI is more commonly seen in preterm and low birth weight babies,[170] and may present with non-specific symptoms of fever, lethargy, apnea, and abdominal distention.[172] Renal involvement can also manifest as rising serum creatinine and non-oliguric renal failure. Oliguria or anuria can be seen as result of obstruction of the urinary tract by a fungus ball (Figure 36.8).

Diagnosis of fungal UTI

Urine culture

Growth of $>10^4$ CFU/ml candida in a single urine culture obtained in a catheterized urine sample is generally considered as diagnostic of candida UTI.[171,172]

Radiology

Abnormalities in renal ultrasound and computerized axial tomography (CAT) scan are described commonly in patients with funguria. In one study, renal candidiasis, defined as renal

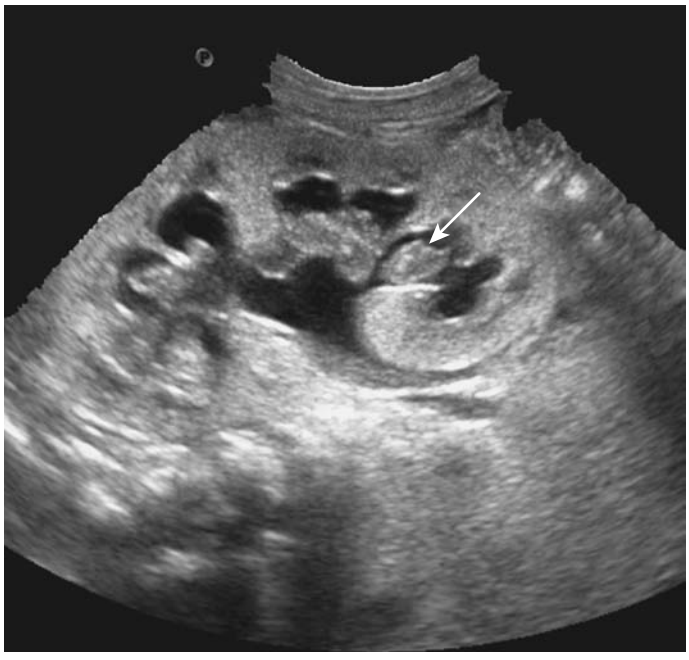

Figure 36.8 Renal ultrasound showing dilated calyces, pelvis, and proximal ureter. An echogenic fungus ball (arrow), is seen in the calyces. The patient's blood and urine grew *Candida parapsilosis*.

fungus balls or a fungal abscess, was reported in 42% (15/36) of patients who underwent renal imaging studies.[170] Of these, 13 had evidence of non-shadowing echogenic foci (fungus ball) and 2 had renal abscess. Using ultrasound, Phillips and Karlowicz identified fungus balls in 35% of infants with candiduria.[171] Because of its portability, ultrasonography can be used as the initial investigative tool for detecting renal lesions, but a CAT scan and/or magnetic resonance imaging (MRI) may also be necessary in some cases.

Treatment of fungal UTI

Candidemia is commonly associated with candiduria. One-third of patients in a series reported by Bryant et al,[170] and 52% of patients studied by Phillips and Karlowicz[171] had candidemia, in association with candiduria. Therefore, systemic antifungal therapy is recommended in the treatment of these patients. Amphotericin B monotherapy is the preferred therapy for candiduria in neonates in the United States.[172,173] In contrast to older children and adults, amphotericin B therapy is well tolerated by neonates.[174] Intravenous amphotericin B is administered at a dose of 1 mg/kg/day. Amphotericin B is preferred to the lipid formulations of amphotericin B in neonates with renal candidiasis, since lipid formulations penetrate renal tubules poorly.[172,175] Renal function and serum electrolytes should be monitored closely in these patients and the amphotericin B dose should be decreased if serum creatinine rises.[172]

The site of infection within the urinary tract and the clinical response determine the length of treatment of funguria. Continued treatment for at least 3 weeks after negative blood and urine cultures are obtained is generally recommended.[176] The mean duration of treatment for renal candidiasis in one study was almost twice the mean duration of treatment for cystitis alone (36 days vs 20 days).[170] A urologist should evaluate patients with obstruction caused by a fungus ball. Surgical intervention is reserved for patients with fungus balls causing severe obstruction of the urinary tract, or for patients with a renal abscess requiring drainage. If necessary, oral fluconazole can be used at a dose of 6 mg/kg/day in candida cystitis, provided the organism is susceptible to this therapy.

Irrigation of the urinary bladder by an aqueous solution of amphotericin B has been used for treatment of uncomplicated fungal infection of the lower urinary tract. Amphotericin is used in a concentration of 50 μg/ml in sterile water. Such therapy has, however, come into question recently. Lack of controlled studies to evaluate the dose and duration of therapy, as well as availability of oral fluconazole as a treatment option, has decreased the attractiveness of amphotericin B bladder irrigation for the treatment of funguria.[177]

Hemorrhagic cystitis

Cystitis associated with microhematuria or gross hematuria can be seen in patients with viral-, chemical-, or radiation-induced inflammation of the urinary bladder. Hemorrhagic cystitis is commonly seen after chemotherapy with cyclophosphamide and ifosfamide, and after bone marrow transplantation. Chemical cystitis associated with cyclophosphamide and ifosfamide therapy occurs within hours to days of chemotherapy, and is more commonly seen during intravenous therapy with cyclophosphamide as compared with oral treatment. On the other hand, late-onset hemorrhagic cystitis seen in patients with bone marrow transplantation is often caused by opportunistic viral infections, and occurs 1–2 weeks after bone marrow transplantation.[178]

Gross hematuria occurs in about two-thirds of patients with cyclophosphamide-induced hemorrhagic cystitis, and microhematuria can be seen in over 90% of cases. Other symptoms include suprapubic pain and dysuria.[179] Suprapubic pain can be intense, sometimes needing narcotic analgesia. Intensive hydration and use of antitoxin therapy with mesna can be effective in preventing hemorrhagic cystitis.[180]

Hemorrhagic cystitis induced by viral infections usually occurs in immunocompromised states, especially after bone marrow transplantation. Viruses associated with late-onset hemorrhagic cystitis in bone marrow transplants are adenovirus, polyoma BK virus, and cytomegalovirus.[178,181]

Diagnosis of viral cystitis is made by detection of viral antigens in the urine. Polymerase chain reaction (PCR) for detection of polyoma BK virus is now commercially available for clinical use.[182,183] Ultrasound examination of the urinary bladder

in hemorrhagic cystitis shows a thickened bladder wall.[184] This finding may resemble the ultrasound features seen in rhabdomyosarcoma of the bladder. Viral cystitis is self-limiting and resolves in about 2–3 weeks. Persistence of ultrasound findings or symptoms is an indication for cystoscopy and biopsy of the bladder wall.

Symptomatic therapy is usually sufficient in hemorrhagic cystitis. Cidofovir, a newer antiviral agent, has been used in the treatment of polyoma BK virus as well as adenoviral hemorrhagic cystitis, but well-controlled studies are lacking.[185] The toxicity profile of this drug limits its use to the most severe cases at this time.

Asymptomatic bacteriuria

Bacteriuria present in children and adults without any clinical manifestations of UTI has been well known. Such covert, or asymptomatic bacteriuria (ABU), can occur in all age groups, including neonates. Except for infancy, ABU is more common in girls than in boys.[1,8,186] Wettergren et al described ABU in 2.5% of unselected boys and 0.9% of girls in infancy.[8] In their landmark epidemiologic study, Kunin and colleagues screened 9878 schoolchildren in Virginia, USA.[1] They reported the prevalence of ABU to be 1.1% in girls and only 0.04% in boys. Similarly, in screening of 13 464 schoolgirls aged 4–18 years old in Newcastle, the prevalence of ABU was noted to be 1.9%. In contrast, the prevalence of ABU in boys was only 0.2%.[186]

The spectrum of organisms isolated in ABU is similar to that associated with symptomatic UTIs. *E. coli* was noted to be the commonest organism (91.7%) in the Newcastle study, followed by *Klebsiella* sp (5.2%), *Proteus mirabilis* (1.2%), and *Streptococcus faecalis*, *Group B Streptococcus*, coagulase-positive staphlococcus (0.4% in each group).[186] *E. coli* causing ABU appear to be less virulent than those causing symptomatic UTI.[187]

Although patients are asymptomatic at the time of initial detection, close evaluation of these children may reveal a history of non-specific symptoms such as urgency, abdominal pain, nocturia, frequency of urination, or generally poor health.[186] Complete absence of recent symptoms has been reported in 24–56% of cases.[1,186] A past history of UTI can be demonstrated in 13–21% of cases.[1,186] Minor structural abnormalities of the urinary tract – such as caliectasis, hydronephrosis, and abnormalities in renal size – have been noted in 10–20% cases.[1,186]

In the past, management of ABU had been controversial. Kunin recommended treatment in order to reduce morbidity associated with UTI.[2] Savage et al demonstrated that antibiotic therapy did not alter long-term recurrence or eradication of bacteriuria.[188] Lindberg et al also noted that despite clearance of bacteriuria by antibiotics, there was no difference in recurrence rate in treated and untreated groups over 3 years of observation.[189] The Newcastle Covert Bacteriuria Study Group also showed similar results of treatment with antibiotics.[190] Based on these observations, patients with ABU need not be treated with antibiotics, unless symptomatic infections are demonstrated.

Long-term outlook of patients with ABU is generally optimistic: 40–50% of children become culture-negative in 2–5 years without any antibiotic therapy.[191] Although up to 15% of patients with ABU may have renal scars when investigated, new scar formation is unusual.[186,192]

Concluding remarks

Infections of the urinary tract are a common childhood disorder that can lead to significant morbidity and hospitalizations. Our understanding of the structural and molecular predispositions to UTI makes it possible to develop a unified diagnostic and therapeutic approach that can be practiced not only in tertiary care centers but also at the level of community physicians treating these patients. Such a unified management approach may result in a lowered long-term risk of renal damage. Newer therapies, such as endoscopic injection of ureteral bulking agents, also offer a fresh opportunity and a challenge to change our approach to VUR and long-term antibiotic regimens in these patients.

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37 Pediatric renal tumors

Eugene Minevich, Curtis A Sheldon, and Martin A Koyle

Tumors of the kidney account for less than 8% of childhood neoplasia. Although the great majority of these are embryonal (mostly Wilms tumors), other malignancies may be seen as well. Both the primary lesion and the effects of chemotherapy have implications for the nephrologist.

Wilms tumor (nephroblastoma)

Wilms tumor (WT), or nephroblastoma, is the most common primary malignant renal neoplasm of childhood. The multidisciplinary approach to this tumor by the National Wilms' Tumor Study Group (NWTSG) and the International Society of Paediatric Oncology (SIOP) has become a model for successful collaborative scientific efforts and cancer treatment. Owing to refinements in surgery, chemotherapy, and radiation therapy, the overall cure rate for WT exceeds 85%. Studies of tumor genetics have laid the foundation for our understanding of tumor suppressor genes and genomic imprinting.

Epidemiology

The annual incidence of Wilms' tumor is 8 cases per million children younger than 15 years, representing 6.3% of cases of childhood cancer.[1] Approximately 450 new cases are diagnosed each year in the United States, making WT the fourth most common pediatric cancer by specific histologic type.[1] Girls have a slightly increased risk of this tumor, with a male-to-female ratio of 0.92 to 1.00. The mean age at diagnosis is 44 months for unilateral disease and 31 months for bilateral disease. WT is rare in the adult population, although numerous cases have been reported.[2]

The majority of cases of WT are sporadic and unilateral. Familial WT is uncommon, occurring in only 1.5% of affected patients.[3] Most cases of familial WT occur in distant relatives, rather than parents or siblings. Sixteen percent of cases of familial WT are bilateral, compared with 7% of sporadic cases. Children with bilateral disease present at a younger age and their mothers tend to be older. Genitourinary anomalies (hypospadias, cryptorchidism, renal fusion anomalies) are present in 4.5% of patients with WT.[4]

Genetics and embryology

WT is believed to result from the abnormal proliferation of the metanephric blastema, without normal differentiation into tubules or glomeruli. Although WT was one of the original paradigms of the Knudson and Strong two-hit model of cancer formation,[5] it has become apparent that several genetic events participate in Wilms tumorigenesis. Wilms tumor 1 (*WT1*) gene, the only suppressor gene identified so far, was recognized as a direct result of the study of children with Wilms' tumor and associated Aniridia, Genitourinary anomalies, and mental Retardation (WAGR syndrome).[6] Cytogenetic analysis of children with WAGR syndrome revealed deletions at chromosome 11p13, which was later found to encompass a contiguous set of genes, including *PAX6*, the gene responsible for aniridia,[7] and *WT1*.[8] *WT1* encodes a transcription factor critical to normal kidney and gonadal development and its deletion in experimental models has been shown to result in major genitourinary maldevelopment.[9] Although germinal deletions or mutations in *WT1* have been documented in almost all patients with WAGR syndrome and the related Denys–Drash syndrome (nephropathy, WT, and pseudohermaphroditism), only a small number of patients with sporadic WT carry *WT1* mutations.[10,11]

A second Wilms' tumor predisposing gene (*WT2*) has been identified at chromosome 11p15, but is not yet cloned.[12] This locus has been proposed based on studies of patients with both WT and Beckwith–Wiedemann syndrome (BWS). BWS is an overgrowth syndrome characterized by high birth weight, macroglossia, organomegaly, hemihypertrophy, neonatal hypoglycemia, abdominal wall defects, and ear pits and creases. Patients with BWS have a 5–10 times increased risk of development of WT but are also predisposed to other malignant tumors, such as hepatoblastoma, neuroblastoma, and rhabdomyosarcoma.[13] Finally, mutations in the *p53* gene are observed in most cases with anaplastic histologic features of WT, implicating a role for this gene in progression from favorable to anaplastic histologic type.[14]

Pathology

The classic histologic pattern is composed of triphasic epithelial, blastemal, and stromal elements (Figure 37.1). Approximately 90% of all renal tumors have the so-called favorable histology (FH). Up to 7% of Wilms' tumors are unfavorable histology, which is characterized by diffuse anaplastic changes, and is a feature that predicts poor outcome. Anaplasia is defined as cells with nuclei having a diameter greater than normal, with increased nuclear content or polyploid mitosis. Clear cell sarcoma of the kidney (CCSK) and rhabdoid tumor of the kidney (RTK) that were previously included as the unfavorable histologic variants of WT are, indeed, clearly separate malignant tumor entities.

Nephrogenic rests

Nephrogenic rests (NR) are foci of embryonal kidney cells that persist abnormally into postnatal life. Histologically, these structures are similar to WT. NR are present in approximately 1% of newborn kidneys and usually regress or differentiate by early childhood.[15] Because NR are present in the kidneys of approximately 40% of patients with WT, it is presumed that the rests represent Wilms' tumor precursors.[16]

Nephroblastomatosis

Nephroblastomatosis is the diffuse or multifocal presence of nephrogenic rests.[17] NR are subdivided into intralobar (ILNR) or perilobar (PLNR), in accordance with their position in the renal lobe.[15] ILNRs are less common and are associated with Wilms' tumor syndromes discovered earlier in life (e.g. WAGR, Denys–Drash syndrome). PLNRs are associated with bilateral tumors and syndromes that present later (e.g. BWS and hemihypertrophy).

Clinical manifestations

The vast majority of patients with WT present with an asymptomatic palpable abdominal mass. They may also present with abdominal pain, gross hematuria, hepatomegaly, varicocele, or lower extremity edema. Hypertension may result from either renal tissue compression, leading to renal ischemia, or from renin production by the tumor itself.[18] A small number of patients who have bled into their tumor may present with signs of hypotension, anemia, and fever. Rarely, patients with advanced-stage disease may present with respiratory symptoms related to the presence of pulmonary metastases. WT has been diagnosed recently in utero with fetal ultrasonography.[19]

Evaluation

Patients at high risk for WT, such as those with syndromes or isolated physical findings – such as aniridia, hemihypertrophy, BWS, WAGR syndrome – require regular, periodic screening with renal ultrasound (US) or a computerized axial tomography (CAT) scan to assure that any asymptomatic tumor is identified prior to it becoming clinically manifested. Laboratory evaluation should include a complete blood cell count, a chemistry profile, including routine electrolytes, with calcium, urinalysis, and coagulation studies.

Radiographic imaging in patients with an abdominal mass must characterize its origin, local extension, and the venous involvement of the tumor. The first imaging study is often a renal US with Doppler technique and it can confirm the location as well as the nature of the tumor (cystic vs solid); it also provides good dynamic imaging of the renal vein and inferior vena cava. An abdominal CAT scan, and occasionally magnetic resonance imaging (MRI), help to further delineate the tumor's origin and extension, lymph node involvement, status of the contralateral kidney for bilateral kidney involvement, invasion into major vessels, or liver metastases (Figure 37.2). The recently available technique of 3-D volume reconstruction can provide tumor anatomy in detail.[20] A chest X-ray and/or a chest CT scan should be performed to evaluate the chest and identify pulmonary metastases,[21] which, if present, upstages the patient, and is important from the perspective of treatment.

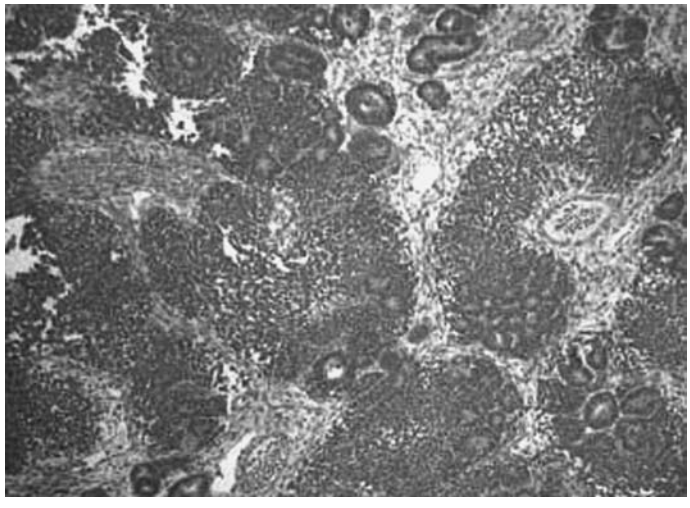

Figure 37.1 Classic triphasic histologic pattern of Wilms' tumor.

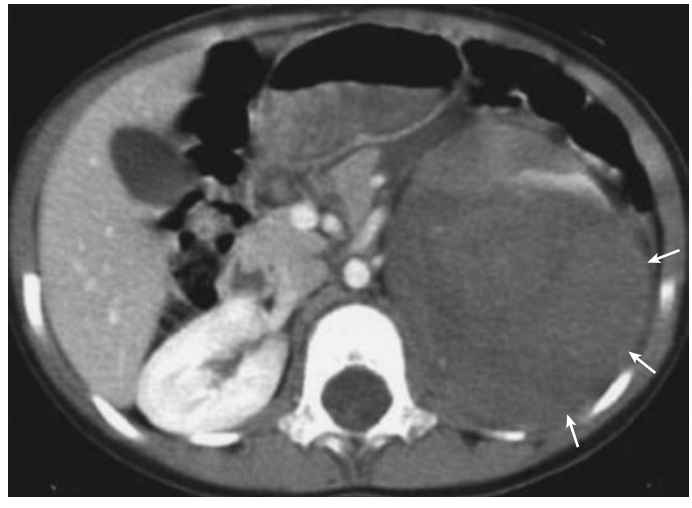

Figure 37.2 Computerized tomography showing Wilms tumor in the left kidney.

Tumor staging

The staging of Wilms tumor is critical in designing therapy and determining prognosis. The most accepted staging system is the one developed by the NWTSG that incorporates clinical, surgical, and pathologic parameters. The NWTSG-V staging of WT is shown in Table 37.1. The NWTSG has further classified WT patients into low-risk and high-risk patients, according to the presence of favorable vs unfavorable histology in the nephrectomy samples.

Surgical therapy

The approach to a patient with Wilms tumor often varies among institutions.[22] Whereas most European SIOP centers make a presumptive diagnosis of WT based on imaging studies alone, some perform needle biopsy first. The SIOP centers prefer to administer prenephrectomy chemotherapy. Over the past 30 years they have shown that preoperative therapy decreases the incidence of tumor rupture during surgery. Therapy also downstages the tumor, and in cases of metastases, also decreases the need for postoperative radiotherapy. The concern with this approach is that chemotherapy may have an impact on the staging of the tumor. Chemotherapy may shrink the tumor or regress the signs of tumor spread, leading to erroneous staging as well as therapy, and exposing these patients to future risk of relapse. In contrast, the NWTSG depends on pathologic and surgical staging in order to predict tumor behavior. Consequently, in North America, patients with suspected Wilms tumor undergo nephrectomy immediately. Both approaches produce comparably high rates of treatment success.

Current recommendations of the NWTSG are to provide preoperative therapy only to children with bilateral disease,[23] tumors that are inoperable at presentation,[24] intravascular tumor extension above the hepatic veins,[25] and a tumor involving a solitary kidney. Pretreatment dramatically reduces tumor thrombus for patients with caval extension[25] and tumor burden, which substantially reduces the surgical morbidity. Patients with bilateral disease,[26] solitary kidney, and those with renal insufficiency or abnormalities of the non-involved kidney, should be considered for a renal-sparing protocol, whenever possible.

Nephrectomy, via a transperitoneal approach, is the initial treatment for unilateral disease where the mass can be completely resected (Figure 37.3). Partial nephrectomy of unilateral Wilms tumor has been explored by some investigators, owing to the possibilities of late occurrence of renal dysfunction and metachronous WT.[27,28] They argue that nephrectomy for unilateral WT increases the risk of hypertension, proteinuria, glomerulosclerosis, and renal insufficiency owing to injuries from hyperfiltration and adjunctive chemotherapy or radiotherapy.[29–31] Most WTs are already too large at initial presentation for a partial nephrectomy, and preoperative chemotherapy is usually necessary if renal-sparing surgery is to be considered.

At the time of surgery, prior to resection of the suspected mass or nephrectomy, both kidneys should be carefully examined. Improved imaging techniques have led to questioning the need for this routine, and may change the surgical therapy in the future to a retroperitoneal flank approach.[32] If a suspicious contralateral lesion is identified, this lesion (as well as the main lesion) should be biopsied. In the presence of contralateral WT, nephrectomy should not be performed. While formal lymph node dissection shows no survival advantages,[33] biopsies should always be performed, since the presence of positive lymph nodes has important prognostic implications.

Table 37.1 National Wilms Tumor Study clinicopathologic staging

Stage I	Tumor limited to kidney and completely excised. No penetration of the renal capsule or involvement of renal sinus vessels
Stage II	Tumor extends beyond the kidney but is completely excised with negative margins and lymph nodes. At least one of the following has occurred: penetration of the renal capsule; invasion of the renal sinus vessels; biopsy of the tumor before removal (except for fine needle aspirate, which may qualify as stage I); and spillage of tumor locally during removal
Stage III	Gross or microscopic residual tumor remains postoperatively (including inoperable tumor, positive surgical margins, diffuse tumor spillage involving peritoneal surfaces), regional lymph node metastasis, or transected tumor thrombus
Stage IV	Hematogenous metastasis or lymph node metastasis outside the abdominal or pelvic cavities
Stage V	Bilateral renal tumors at diagnosis

Neville and Ritchey.[36]

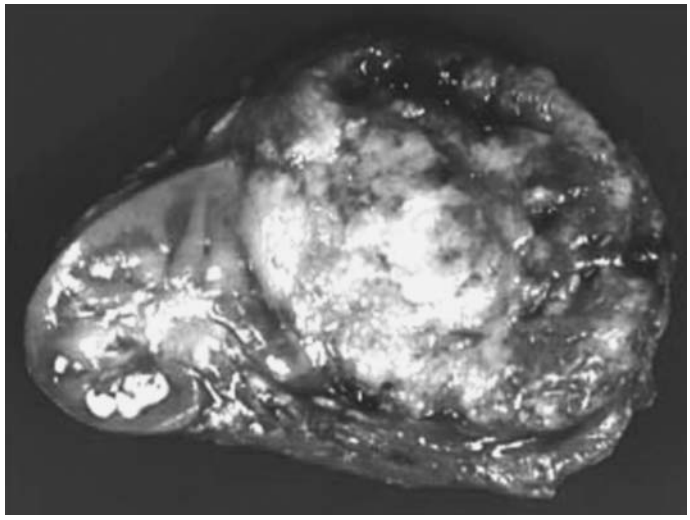

Figure 37.3 Wilms tumor in lower pole of the kidney.

Surgical management becomes more controversial in the case of unilateral multiple NR. Their histologic appearance may be indistinguishable from WT. Thus, the growth pattern of the lesion, as seen on serial imaging, may be the best indication of the need for a nephrectomy. Accordingly, serial imaging is important in planning appropriate intervention and avoiding unnecessary surgery. However, for children presenting with diffuse hyperplastic PLNR, seen as a ring surrounding the entire kidney, surgery should be considered due to the high risk of WT. Most of these cases present with bilateral disease, and partial nephrectomy may be considered.

The major complications of surgical therapy have continued to decrease. A recent review of the records of patients in NWTSG-IV found an 11% incidence of surgical complications after nephrectomy.[34] The most common complications were hemorrhage and small bowel obstruction. Risk factors associated with increased surgical complications are higher local tumor stage, intravascular extension, en bloc resection of other visceral organs, and incorrect preoperative diagnosis.[35]

Post-surgical treatment

Consecutive trials of the NWTSG, beginning in the late 1960s, provided critical insights into the role of adjuvant therapy for Wilms' tumor. The intergroup studies have sought to refine adjuvant therapy regimens, with each study intensifying the therapy provided to high-risk patients and decreasing or modifying the therapy to lower-risk patients.[36] NWTSG-I and II revealed that postoperative radiation was unnecessary in stage I disease and that the combined use of vincristine and dactinomycin was more efficacious than either drug alone. NWTSG-III showed that patients with stage II tumors with FH can be treated without abdominal irradiation if vincristine and dactinomycin are administered. This study also revealed that the addition of doxorubicin to the two-drug regimen improves outcome in stage III and IV disease with FH.

The last of the NWTSGs showed that pulse-intensive therapy is equally efficacious, less toxic, and more cost-effective than the conventional regimen, with an overall 4-year survival rate of patients with FH approaching 90%.[37] The ongoing NWTSG-V was designed to define possible roles of gene expression in identifying those patients at greater risk for relapse.[36] It seeks to determine whether adjuvant chemotherapy provides benefit to children younger than 24 months who have small stage I tumors with favorable histologic feature. The current treatment algorithm of WT, based on its stage and histology, is shown in Table 37.2.

Bilateral Wilms tumor

Bilateral disease occurs in approximately 5–10% of patients with WT. These children pose a therapeutic challenge because of the difficulty in obtaining local cure, while sparing renal parenchyma. Compared with patients with unilateral WT, patients with bilateral tumors have an increased rate of chronic renal failure and end-stage renal disease (ESRD) – estimated to be 3.8% among patients treated in NWTSG-IV.[38] The most common cause of renal failure in this patient group is nephrectomy due to tumor progression, or recurrence.

In a child with bilateral WT, bilateral biopsy specimens should be obtained to confirm the presence of WT in both kidneys and establish the histologic type of each tumor. If the tumor is identified in both kidneys, patients should be given preoperative chemotherapy that is appropriate to the stage and histology. After 6 weeks of chemotherapy, the patient should be reassessed with abdominal CT to determine the feasibility of resection. If the tumor has decreased in size, partial nephrectomy may be performed. If the tumor persists, additional chemotherapy and radiation should be considered. Survival of patients undergoing initial biopsy followed by postoperative chemotherapy is equivalent (83% at 2 years) to patients undergoing initial surgical resection.[39] Bilateral nephrectomies are needed rarely. A mandatory waiting period of 1–2 years should elapse before kidney transplantation is considered for these patients.

Recurrent Wilms tumor

With refinement of treatment modalities, the cure rate for WT tumor is in excess of 85%.[40] However, 10–15% of patients with FH, and 50% of patients with anaplastic tumors experience primary progression or tumor recurrence. Most relapses are diagnosed within the first 2 years after original diagnosis. The most common site of recurrence is the lung, tumor bed, the liver, bone, and lymph nodes.

Approximately 1% of children presenting initially with unilateral WT develop metachronous bilateral disease.[28] Patients with nephrogenic rests, in particular PLNR in children younger than 12 months at the time of diagnosis, have a significantly

Table 37.2 Treatment protocol for National Wilms' Tumor Study – V

Stage, histology	Surgery	Chemotherapy	Radiotherapy[a]
Stage I or II with FH Stage I with anaplasia	Nephrectomy	Dactinomycin, vincristine (18 weeks)	No
Stage III or IV with FH Stage II–IV with focal anaplasia	Nephrectomy	Dactinomycin Doxorubicin, vincristine (24 weeks)	Yes
Stage II–IV with diffuse anaplasia Stage I–IV CCSK	Nephrectomy	Vincristine Doxorubicin Cyclophosphamide Etoposide (24 weeks)	Yes
Stage I–IV RTK	Nephrectomy	Cyclophosphamide Carboplatin Etoposide (24 weeks)	Yes

FH, favorable histology; CCSK, clear cell carcinoma of the kidney; RTK, rhabdoid tumor of the kidney.
[a]Current radiotherapy dosage is approximately 1080 cGy for the abdomen and 1200 cGy for the lung. Only patients with stage IV with lung metastases receive whole lung radiotherapy.
Neville and Ritchey.[36]

increased risk of developing a contralateral tumor. As a result, some authors have recommended more frequent surveillance for this group of patients.[28] With aggressive therapy, up to 80% of patients with recurrent WT and favorable prognostic features can be cured. Factors associated with positive outcome include favorable histologic features, initial treatment with only vincristine and dactinomycin, relapse to the lungs only, relapse in the abdomen of a patient who did not receive abdominal irradiation, and relapse more than 12 months after the original diagnosis.[41,42] In order to improve outcomes, several different regimens have been tried, including salvage chemotherapy with ifosfamide, platinum, and etoposide, with response rates up to 72%.[42,43] In addition, some patients have been treated with high-dose chemotherapy followed by autologous hematopoietic stem-cell rescue.[44]

Late effects of treatment

Numerous organ systems are subject to the late sequelae of anticancer therapy. The late effects of WT treatment have received considerable attention because WT is usually curable, and there is a growing number of long-term survivors. Renal function can be affected by several modalities of treatment, including nephrectomy, chemotherapy (especially that used to treat recurrent disease), and radiation. Although most WT survivors have only one kidney, only 0.25% of patients were found to have renal failure.[38] The median interval from diagnosis of WT to onset of chronic renal failure is 21 months. Renal failure is most prevalent in patients with bilateral WT.

Another well-recognized long-term effect of WT therapy is congestive heart failure (CHF), which is found to have a cumulative frequency of 4.4% of patients, 20 years after diagnosis of WT in patients initially treated with doxorubicin.[45] Risk factors for CHF included increasing cumulative doxorubicin dose and radiation to the lung and left hemiabdomen. An analysis of pregnancy outcome among WT survivors reveals that women who received flank radiation therapy are at increased risk of fetal malposition, premature labor, low birth weight, and occurrence of congenital malformations.[46] Gonadal irradiation can produce hypogonadism and temporary azoospermia in boys.[47] In females, the main therapeutic modality resulting in ovarian dysfunction is radiation.[48] Finally, the cumulative incidence of secondary malignancy in Wilms' tumor survivors is 1.6%, 15 years after diagnosis of primary tumor.[49]

Clear cell sarcoma

Clear cell sarcoma of the kidney is currently considered distinct from Wilms' tumor. The peak incidence of this tumor is between 3 and 5 years of age. Unlike WT, CCSK is associated with bone and brain metastases in 40–60% cases. Bilateral involvement has thus far not been reported, and it is not associated with the congenital anomalies commonly seen with WT. The classic histologic pattern consists of a cellular lesion of polygonal cells with round oval nuclei that have a delicate chromatin pattern and indistinct nucleoli.[50] NWTSG-V recommends that CCSK be treated at all stages with the same therapeutic regimens as used for Wilms' tumor with diffuse anaplasia (excluding stage I). Expected 4-year survival is 75%.[51] Important predictors of improved survival are lower stage, younger age at diagnosis, and absence of tumor necrosis.[52]

Rhabdoid tumor of the kidney

Rhabdoid tumor of the kidney was formerly categorized as an unfavorable histologic pattern of WT. It accounts for 2% of

the renal tumors registered in the NWTSG. Histologically, it is characterized by large cells with abundant acidophilic cytoplasm, frequently containing a discrete zone of pale eosinophilia, made up of fibrillary inclusion bodies. Nuclei are large, with prominent nucleoli.

The tumor is typically large, often replacing the entire kidney. It presents early in life and the median age at presentation is 11 months, with more than 50% of patients aged <1 year. Metastases may be found not only in the lungs and liver but also, unlike WT, in the brain.[53] In addition, RTK may be associated with a second primary tumor in the brain in 10–15% patients, the most common type being medulloblastoma. RTK is the most aggressive and lethal childhood renal tumor, with overall mortality of 80%.[53] The current treatment protocol consists of nephrectomy, followed by chemotherapy with carboplatinum, etoposide, and cyclophosphamide for 24 weeks, and radiotherapy.

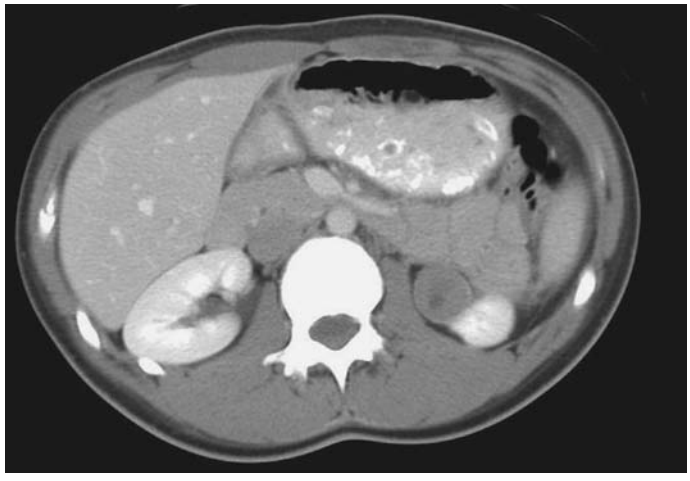

Figure 37.4 Computerized tomography showing renal cell carcinoma in the left Kidney.

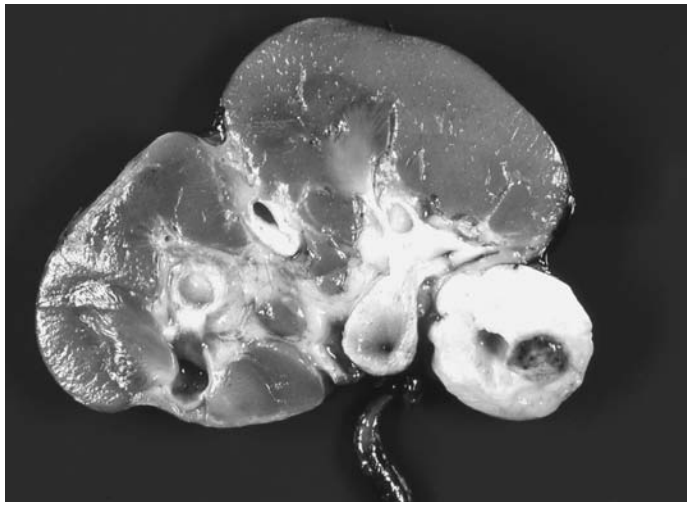

Figure 37.5 Lower pole of the left kidney renal cell carcinoma.

Renal cell carcinoma

Renal cell carcinoma (RCC) is an uncommon renal epithelial malignant tumor in children. It represents 2–5% of primary renal malignant tumors of childhood.[54] Childhood RCC may resemble the adult clear cell and papillary subtypes (Figures 37.4–37.6).[55] RCC has been reported in infancy, but most patients are older, with a mean age of 9–15 years. Most children present with an abdominal mass (24–55%), hematuria (42%), and pain (32%). Children also may have hypertension, fever, weight loss, and polycythemia.[56] Approximately 25% of children with RCC have distant metastatic disease at presentation, most commonly to the lung, liver, and bone. Imaging studies cannot differentiate RCC from other renal tumors.

The most significant prognostic variable for survival of pediatric patients with RCC is a complete resection and low-stage disease.[57] Survival for patients presenting with stage I disease is greater than 90%, for patients with stage II and III disease approximately 50%, and for patients with stage IV disease almost 0%. The tumor is not responsive to radiotherapy, and no effective chemotherapy is available for non-localized or relapsed disease.

Congenital mesoblastic nephroma

Congenital mesoblastic nephroma (CMN) is the most common renal tumor in infants, with a mean age of 3.5 months at diagnosis.[58] CMN occurs in two forms:

- A typical (fibromatous) type is seen almost exclusively in infants under the age of 3 months; this is a benign tumor.
- An atypical (cellular) variety is usually seen in older children but also occurs in infants; this is a potentially malignant tumor that is capable of recurrence and metastasis.[59,60]

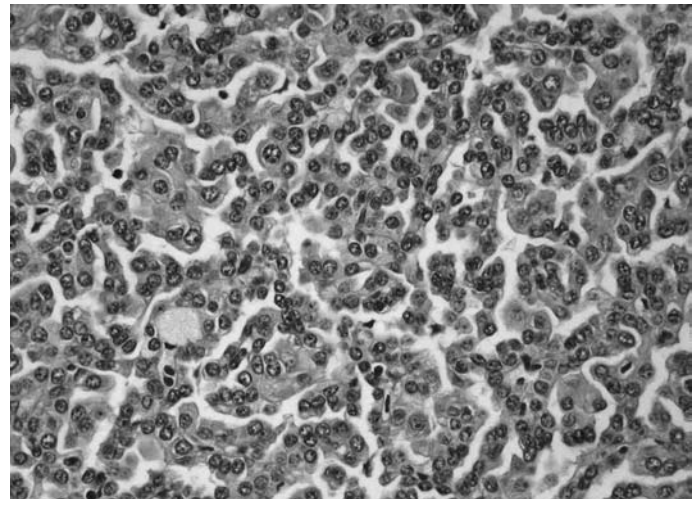

Figure 37.6 Histological appearance of renal cell carcinoma.

Hypertension may occur from renin hypersecretion.[61] Hypercalcemia also has been reported, owing to tumor secretion of prostaglandin.[59] Nephrectomy alone seems to be adequate treatment for infants < 3 months of age, and possibly may be considered even for older patients with typical fibrous histology. Chemotherapy with a WT regimen should be considered for patients with incomplete resection, more aggressive cellular features, and a high mitotic index, and for any patient with evidence of metastasis or recurrence. Partial nephrectomy should not be performed, since the risk of local recurrence is high, owing to the tumor's tendency to infiltrate the surrounding renal parenchyma.

Angiomyolipoma

Angiomyolipoma is a benign, hamartoma-like mass composed of smooth muscle, blood vessels, and fat. This lesion is seen almost exclusively in children with tuberous sclerosis, a condition characterized by mental retardation, seizures, glial nodules in the brain, adenoma sebaceum, phakoma of the retina, and hamartomas of the liver, heart, bone, or kidney. It is estimated that 80% of patients with tuberous sclerosis complex have angiomyolipomas, and that the frequency increases with age.[62] Tumors are often bilateral and multifocal. Females appear to be more susceptible to multiple and larger-size tumors when compared with males. Hormonal influences (progesterone receptors in the smooth muscle cells of angiomyolipomas) may offer an explanation to the gender differences in tumor growth at puberty.

Most angiomyolipomas are < 4 cm in size and can be asymptomatic. Larger tumors are at risk for hemorrhage.[63] Management should be non-operative, with periodic re-imaging for small asymptomatic lesions. Nephron-sparing approaches are recommended for children with large or symptomatic tumors. Angioinfarction of amenable lesions or partial nephrectomy should be considered.

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Appendix

To convert conventional units to SI units, multiply by the conversion factor

Test	Conventional unit	Conversion Factor	SI Unit
Electrolytes and Common Assays			
Sodium	mEq/L	1.0	mmol/L
Potassium	mEq/L	1.0	mmol/L
Chloride	mEq/L	1.0	mmol/L
Bicarbonate	mEq/L	1.0	mmol/L
Anion gap	mEq/L	1.0	mmol/L
Calcium	mg/dl	0.25	mmol/L
Phosphorus	mg/dl	0.323	mmol/L
Magnesium	mg/dl	0.411	mmol/L
Urea nitrogen (BUN)	mg/dl	0.357	mmol/L
Creatinine	mg/dl	88.4	µmol/L
Creatinine Clearance	ml/min	0.0167	ml/s
Uric acid	mg/dl	59.48	µmol/L
Glucose	mg/dl	0.0555	mmol/L
Osmolality	mOsm/kg	1.0	mmol/kg
Proteins			
Protein-total	g/dl	10.0	g/L
Albumin	g/dl	10.0	g/L
Immunoglobulin			
G	mg/dl	0.01	g/L
A	mg/dl	0.01	g/L
M	mg/dl	0.01	g/L
D	mg/dl	10.0	mg/L
E	mg/dl	10.0	mg/L
C3 Complement	mg/dl	0.01	g/L
C4 Complement	mg/dl	0.01	g/L
Myoglobin	µg/L	0.0571	nmol/L
Lipids			
Lipids-Total	mg/dl	0.01	g/L
Cholesterol –Total	mg/dl	0.0259	mmol/L
HDL Cholesterol	mg/dl	0.0259	mmol/L
LDL-Cholesterol	mg/dl	0.0259	mmol/L
Triglycerides	mg/dl	0.0113	mmol/L
Miscellaneous			
Ammonia	µg/dl	0.587	µmol/L
Citrate	mg/dl	52.05	µmol/L
Ferritin	ng/ml	2.247	pmol/L
Iron	µg/dl	0.179	µmol/L
Iron binding capacity-Total	µg/dl	0.179	µmol/L
Lactate	mg/dl	0.111	mmol/L
Oxalate	mg/L	11.1	µmol/L
Transferrin	mg/dl	0.01	g/L
Pancreatic Enzymes			
Amylase	units/L	1.0	U/L
Lipase	units/L	1.0	U/L

Test	Conventional unit	Conversion Factor	SI Unit
Liver Functions			
Alkaline phosphatase	units/L	1.0	U/L
Alanine aminotransferase (ALT)	units/L	1.0	U/L
Aspartate aminotransferase (AST)	units/L	1.0	U/L
Bilirubin	mg/dl	17.1	µmol/L
γ-Glutamyltransferase (GGT)	units/L	1.0	U/L
Lactate dehydrogenase (LDH)	units/L	1.0	U/L
Hormones			
Bone and Divalent Ion Related			
Calcitonin	pg/ml	1.0	ng/L
Parathyroid hormone	pg/ml	1.0	ng/L
Vitamin D			
1-25, Dihydroxy-Vitamin D3	pg/ml	2.6	pmol/L
25, Hydroxy-Vitamin D3	ng/ml	2.496	nmol/L
Renin-Angiotensin System			
Angiotensin I	pg/ml	0.772	pmol/L
Angiotensin II	pg/ml	0.957	pmol/L
Aldosterone	ng/dl	0.0277	nmol/L
Antidiuretic hormone	pg/ml	0.923	pmol/L
Renin	pg/ml	0.0237	pmol/L
Growth Hormones			
Somatostatin	pg/ml	0.611	pmol/L
Somatostatin –C (Insulin-like growth factor)	ng/ml	0.131	nmol/L
Adrenal			
Cortisol	µg/dl	27.59	nmol/L
Epinephrine	pg/ml	5.46	pmol/L
Norepinephrine	pg/ml	0.00591	nmol/L
Hematologic			
ESR	mm/h	1.0	mm/h
Hemoglobin	g/dl	10	g/L
WBC count	x 10^3/µL	1.0	x 10^9/L
Reticulocyte count	% of RBC	0.01	Proportion of 1.0

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Index

Clinical Pediatric Nephrology

Second Edition

Fully revised and expanding upon the highly successful first edition, *Clinical Pediatric Nephrology* is a practical clinical resource that boasts a worldwide array of contributors, including the most prominent pediatric nephrologists in the US.

Outstandingly illustrated with a combination of radiological, pathological and anatomical images, the book is well structured into several specific areas, including:

- the structure and renal physiology of the kidney
- the epidemiology of pediatric renal disease
- parenchymal diseases
- diseases of tubular transport
- renal failure
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Also featuring expanded case histories relating to the discussion and management of renal disease, *Clinical Pediatric Nephrology* will be highly valued as an informative and extremely useful reference tool for nephrologists and house officers in practice, as well as nephrology fellows in training.

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