CHAPTER

64 A Clinical Approach to Kidney Disease in Infants, Children, and Adolescents

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THE EXPRESSION OF "KIDNEY DISEASE" IN CHILDREN

This chapter is intended for medical professionals who are not pediatric nephrologists or pediatricians but who may be called on to evaluate the infant, child, or adolescent patient for the possible presence of kidney disease. Therefore, it is not possible to include an in-depth discussion of all diseases of the specialty and, in particular, the chapter avoids discussions of therapy in most because confirmation of a certain diagnosis of childhood kidney disease would lead the concerned practitioner to consult with a pediatric nephrologist for definitive and ongoing care.

The fundamental difference between pediatric and adult patients is the capacity and, indeed, the expectation of somatic growth and development from infancy through late adolescence, as compared to homeostasis of body mass in the adult. The appearance of kidney disease in childhood interferes with the normalcy of those pediatric processes leading to undisturbed growth (failure to thrive). The pattern of growth from birth through first consultation, plotted formally on available charts of normal patterns of gain in height, height velocity, body mass, and, in children less than 36 months, head circumference, must be a high-ranking task in evaluation of the patient for possible chronic kidney disease (CKD). Absence of changes do not rule out all causes of kidney disease, as discussed throughout the chapter by category of disease, but its presence may help the astute clinician in differential diagnosis.

For ease, and as we teach and practice, children present with a limited, but understandable, series of specific features that alert the clinician to the presence of "kidney disease." Table 64.1 encompasses all topics discussed in this chapter. Understanding the limitations of the chapter, it is hoped the reader will still find the text useful in everyday consultation and practice.

There are common elements to a history and physical examination of the infant, child, and adolescent when thinking about the presence of kidney disease, and those are summarized in Table 64.2.

Measurement of Kidney Filtering Function[1,2]

Assessment of glomerular filtration rate (GFR) is the single most important test of renal function required in clinical practice. The 24-hour endogenous creatinine clearance is used in adults, but such urine collections can be difficult to obtain in infants and young children, particularly those who are outpatients. The 24-hour urine excretion of creatinine is a measure of creatinine production that is related to muscle mass, and in turn correlates with the cube of height in boys and girls from the age of 6 months to maturity. Because GFR correlates with body surface area (BSA) or the square of height, it follows that GFR corrected for BSA is related to height. Thus,

$$\text{GFR} = \frac{\text{UcrV}}{\text{Pcr}} \quad (1)$$

$$\text{UcrV} \,\alpha\, \text{height}^3 \quad (2)$$

$$\text{GFR} \,\alpha\, \text{height}^2 \quad (3)$$

$$\frac{\text{GFR}}{\text{BSA}} \,\alpha\, \frac{\text{height}}{\text{Pcr}} \text{ or } \frac{\text{GFR}}{\text{BSA}} = \frac{\text{height}}{\text{Pcr}} \quad (4)$$

where V is urine flow rate and Ucr and Pcr are the urine and plasma concentrations of creatinine, respectively. The value for the constant k has been empirically based on measured GFR from iohexol-based GFR studies, and reinterpreted as the creatinine assay itself is now standardized around the world (bedside Chronic Kidney Disease in Children Prospective Cohort Study [CKiD]).

$$\text{GFR (mL/minute/1.73 m}^2) = 0.413 \times \text{height (cm)/Pcr (mg/dL)} \quad (5)$$

With the newer assays for serum creatinine in infants younger than age 1 year, and in adolescents older than 18 years, Equation 64.5 has not been validated. Due to the difficulty associated with 24-hour urine collection in young children, estimates of GFR from the height and plasma creatinine may be more reliable than the 24-hour endogenous clearance in

64.1 Major Features of the Presentation of Kidney Disease in Childhood

- Failure to thrive
- Chronic metabolic acidosis
- Chronic metabolic alkalosis
- Kidney Fanconi syndrome
- Hyponatremia
- Hypokalemia
- Hyperkalemia
- Edema
- Hematuria
- Proteinuria
- Hypertension
- Hypophosphatemia
- Hyperphosphatemia
- Hypocomplementemia
- Nephrolithiasis
- Rickets
- Recurrent volume depletion
- Polyuria
- Oliguria
- Recurrent urinary infection
- Abdominal masses
- Dysuria, frequency
- Disorders of sexual differentiation
- Hypercalcemia
- Hypocalcemia
- Hypomagnesemia
- Thrombotic microangiopathy

children and obviously are more convenient. It is important to note that this method is likely unreliable when the normal relation between muscle mass and height is altered, as in malnutrition or muscular dystrophy, or in severe renal failure when tubular secretion of creatinine is increased.

Plasma creatinine concentration averages 0.88 mg per dL at birth, when the level is largely determined by the mother's plasma creatinine concentration. It falls to a nadir of 0.32 mg per dL at 2 years as GFR increases and then rises with the increase in muscle mass. From age 2 weeks to 5 years, a normal blood creatinine level is between 0.11 and 0.35 mg per dL. From 5 to 10 years, a normal blood creatinine level is between 0.28 and 0.55 mg per dL. Normal serum creatinine may be as high as 0.84 to 0.93 mg per dL in older teenagers or adult men. However, a serum creatinine concentration greater than 1.10 to 1.20 mg per dL should raise concern for underlying renal disease. Clinical paradigms for measured GFR (mGFR) using iohexol are evolving quickly in the pediatric nephrology clinics.

The addition of other agents such as cystatin C into the estimated GFR (eGFR) equation may improve precision, but not offer substantial important information when the mGFR is above 75 mL/min/1.73 m^2. Adolescents of adult size may benefit from the MDRD equation used in adults for determination of eGFR.

Genetics and Pediatric Kidney Diseases[3]

The expression of monogenic mutations is not infrequent in a variety of chronic kidney diseases in pediatrics, and encompasses the entire clinical spectrum of such disorders, from congenital anomalies of the kidney and urinary tract (CAKUT), glomerular and tubular disorders, through specific transport defects of single, selected ions, minerals, or other substances. As a result of the sequencing of the human genome, and the use of advanced techniques including high throughput technologies, rapid discoveries are made daily. As a result of the rapidity of mutational gene discoveries linked to pediatric kidney disease expression in patients, a comprehensive listing is immediately out of date. However, up-to-date knowledge of such findings can be learned from Online Mendelian Inheritance in Man (OMIM; http://www.omim.org/). Currently known mutations for monogenic disorders and CAKUT are shown in Tables 64.3 and 64.4, respectively. Throughout this chapter, diseases referred to may be found in this listing with a hyperlink about them.

Embryogenesis of the kidney and urinary tract has been advanced at the molecular level considerably in the recent past, and explains, in part, many of the well-recognized malformation complexes seen in patients ranging from infancy (e.g., aplasia, hypoplasia, dysplasia, cystic diseases) through later adolescence (e.g., autosomal-dominant polycystic kidney disease, autosomal-recessive nephrolithiasis with kidney failure/Dents disease). Alternatively, sporadic urologic malformations, the third most common birth defect overall in live-born neonates (e.g., posterior urethral valves, hydronephrosis), may not have easy to decipher molecular pathophysiology, but must be remembered not only in infancy, but during the entire spectrum of pediatrics, as their consequences may only be revealed in the older child or adolescent with the appearance of progressive CKD.

As in adult CKD, polygenic factors play a role in the expression of other disorders, or in their severity of expression. Little information that is different for pediatric CKD when compared to adult disease is available now, and the reader is referred to other chapters in this volume for a discussion of the topic.

HEMATURIA

Hematuria is one of the most common urinary symptoms in children, and may represent a benign condition such as hematuria resulting from strenuous exercise or from a life threatening illness such as Wilms tumor. Hematuria originating from glomerulonephritis (GN) is often signified by coco-cola- or tea-colored urine, red blood cell casts, and/or dysmorphic red blood cells (RBCs), whereas bleeding distal to the glomerulus, such as from urologic issues or infections, are more likely to be associated with red urine and end of void hematuria.

History

Abdominal, flank, or groin pain is suggestive of nephrolithiasis. Dysuria, foul smelling urine, urgency, and increased voiding frequency with or without fever may denote a urinary tract infection (UTI) that is usually caused by gram-negative bacteria or adenovirus in children outside of infancy

64.2 Common Elements of the Pediatric History and Physical Examination

History	Physical Examination
Birth History: complete maternal obstetric history; birth weight, length, and head circumference; gestational age; placental abnormalities; neonatal history of illness and medications; malformations outside the kidney	Growth percentiles for length, body mass (weight), head circumference (through 2 years of age; http://www.cdc.gov/growthcharts/)
Feeding and Dietary History: source of protein intake (breast, formula); food allergies; food avoidances; urination pattern (frequency, stream appearance); defecation pattern	Blood pressure with appropriate size cuff, and if concern over hypertension, four extremity blood pressure at first consultation; plot normative values for measured arm blood pressure for boys and girls, respectively: http://www.cc.nih.gov/ccc/pedweb/pedsstaff/bptable1.PDF http://www.cc.nih.gov/ccc/pedweb/pedsstaff/bptable2.PDF
Family History: chronic kidney diseases, kidney rransplantation; hypertension; cystic kidney diseases; kidney stones; infant deaths; fractures in young adults; early onset osteoporosis; "unusual diseases"; early onset myocardial infarction, stroke	Complete Physical Examination, with special emphasis depending on the reason for consultation to: skin lesions, rashes, or purpura; peripheral edema; retinal examination for pigmentary changes, anterior chamber for crystal deposits, abnormalities of the eye; alterations of ears (location on the skull relative to the palpebral fissures; size and/or malformations); vascular bruits including abdominal aorta, renal artery locations; abdominal masses; organomegaly; sexual development, feminization, or masculinization of the opposite gender, Tanner sexual maturity rating; presence of arthritis or arthralgias; muscle tone; numbers of fingers and toes; scoliosis; rachitic changes of the extremities, chest and/or skull
Complete Review of Ten Systems	
Social History: developmental milestone achievements; school performance	A listing of relevant milestones by age can be accessed here: http://www.cdc.gov/ncbddd/actearly/milestones/
Immunization History	Schedules and recommendations by age can be accessed here: http://www.healthychildren.org/english/tips-tools/pages/default.aspx?nfstatus=401&nftoken=00000000–0000–0000–0000–000000000000&nfstatusdescription=ERROR:+No+local+token - immunization-schedules

or, alternatively, may represent the presence of hypercalciuria. Abdominal trauma may induce hematuria especially in abnormally shaped kidneys of polycystic or hydronephrotic nature. In postinfectious GN there is a window of at least a week between the occurrence of the febrile disease, most commonly streptococcal pharyngitis or impetigo, to the onset of tea-colored urine, whereas in immunoglobulin A (IgA) nephropathy, another common cause of acute glomerulonephritis in children, a febrile prodrome precedes renal symptoms by only 2 to 3 days. The review of systems is imperative in a child with hematuria as the differential diagnosis includes systemic lupus erythematosus (SLE) and other vasculitides. Alport syndrome, sickle cell disease, and benign familial hematuria are examples of hereditary conditions associated with microscopic hematuria. It is very unlikely for coagulopathic states to manifest as hematuria alone, although a history of bleeding disorder should be sought.

Physical Exam

Periorbital and facial edema are suggestive of GN. The joints and skin should be examined for involvement in vasculitis. Intravascular volume contraction, especially in infancy, can predispose to renal vein thrombosis that may present with gross or microscopic hematuria.

64.3 Selected Monogenic Kidney Disorders

Disorder	Inheritance	OMIM	Gene(s)
Congenital nephrotic syndrome	AR	256300	NPHS1, LAMB2, PLCE1
WT-1 related disorders	AR	256370	WT1
Steroid-resistant nephrotic syndrome	AR	600995	NPHS2, LAMB2
FSGS1	AD	603278	ACTN4
FSGS2	AD	603965	TRPC6
FSGS3	AD	607832	CD2AP
Alport syndrome	X-linked AR AD	301050 203780 104200	COL4A5 COL4A3, COL4A4 COL4A3, COL4A4
ADPKD	AD	173900	PKD1, PKD2
ARPKD	AR	263200	PKHD1
NPHP NPHP1 NPHP2 NPHP3 NPHP4 NPHP5–7	AR	 256100 602088 604387 606966	 NPHP1 NPHP2/INVS NPHP3 NPHP4 NPHP5,NPHP6/CEP290, NPHP7/GLIS2
MCKD	AD	603860	UMOD (MCKD2)
Cystinosis	AR	219800	CTNS
Lowe syndrome	X-linked	309000	OCRL
Dents disease	X-linked	300009	CLCN5, OCRL
Cystinuria	AR	220100	SLC3A1, SLC7A9
Bartter syndrome Type I Type II Type III Type IV	AR	 601678 241200 607364 602522	 SLC12A1/CLCNKB KCNJ1 CLCNKB BSND
Gitelman syndrome	AR	263800	SLC12A3
Liddle syndrome	AD	177200	SCNN1B, SCNN1G
GRA	AD	103900	CYP11B2, CYP11B1
Apparent mineralocorticoid excess	AR	218030	HSD11B2
Distal RTA . . .with progressive deafness	AD AR AR	179800 602722 267300	SLC4A1 ATP6V0A4, SLC4A1 ATP6V0A4, ATP6V1B1
Osteopetrosis with RTA	AR	259730	CA2

(continued)

64.3 Selected Monogenic Kidney Disorders (continued)

Disorder	Inheritance	OMIM	Gene(s)
Nephrogenic diabetes insipidus			
	X-linked	304800	AVPR2
	AR, AD	125800	AQP2
Primary hyperoxaluria			
Type 1	AR	259900	AGXT
Type 2	AR	260000	GRHPR
Type 3	AR	613616	DHDPSL (HOGA1)

AD, autosomal dominant; AR, autosomal recessive; ADPKD, autosomal-dominant polycystic kidney disease; FSGS, focal and segmental glomerulosclerosis; GRA, glucocorticoid-remediable aldosteronism; MCKD, medullary cystic kidney disease; NPHP, nephronophthisis; OMIM, On-line Mendelian inheritance in man (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim); RTA, renal tubular acidosis.

64.4 Monogenic Disorders Producing CAKUT

Type of Malformation	Cause	Anatomic and Histologic Charateristics	Gene
Renal agenesis	No interactions between the UB and MM	Absence of the ureter and kidney	Ret, GDNF
Renal hypoplasia	Aberrant interactions among the UB, MM, or stroma	Reduced number of UB branches and nephrons that are fully formed, small kidney size	Pax2, Sall1 Six2, BMP4 HNF1β UMOD
Renal dysplasia	Aberrant interactions among the UB, MM, or stroma	Reduced number of UB branches and nephrons. Presence of undifferentiated stromal and mesenchymal cells, cysts, or cartilage. Frequently associated with kidney hypoplasia	Pax2 HNF1β UMOD Nphp1 BMP4, Six2 XPNPEP3
Polycystic kidneys	Aberrant tubular and collecting duct patterning	Cysts in tubules and collecting ducts Normally formed glomeruli	Pkd1, Pkd2 HNF1β HPHP1
Multicystic dysplastic kidneys	Aberrant interactions among the UB, MM, or stroma	Absence of glomeruli and tubules Presence of large cysts Aberrant patterning Poorly formed atretic ureters Small remnant kidney (if organ involutes)	HNF1β UPIIIA
Medullary cystic kidney disease 2	Aberrant tubular and collecting-duct patterning	Tubular atrophy, interstitial fibrosis, cysts in distal tubules and medullary collecting ducts	UMOD
Duplex ureters	Supernumerary UB budding from the ND	Duplex ureters and kidneys or duplex ureters and collecting systems May be associated with VUR or obstruction if UB budding is ectopic	Robo2 FoxC1 FoxC2 BMP4
Horseshoe kidney	Defects in renal capsule	Kidneys are fused at inferior lobes and located lower than usual	HNF1β

UB, ureteric bud; MM, metanephric mesenchyme; ND, nephric duct.

Laboratory

In evaluation of hematuria, the urine should be examined both by dipstick and under a microscope. A positive urine dipstick for blood in the absence of RBC under the microscope suggests other causes of pigmenturia, such as hemoglobinuria or myoglobinuria. The presence of proteinuria (the dipstick is qualitative) is consistent with GN. Hematuria with low complement levels should raise the diagnosis of postinfectious GN, atypical hemolytic uremic syndrome, membranoproliferative GN, and GN associated with ventricular-peritoneal shunt infection and endocarditis. Increased calcium to creatinine ratio (>0.4) may signify the presence of hypercalciuria, a common condition leading to microscopic hematuria in childhood, and prompt an evaluation discussed in that section of this chapter.

Imaging

A kidney ultrasound is mandatory in the evaluation of hematuria, and further imaging should be ordered as required by the working diagnosis. As a general rule, intravenous pyelography has been replaced by other imaging modalities. Care should be taken in ordering imaging beyond the kidney ultrasound because all the side effects seen in adults with kidney disease (e.g., contrast nephropathy; nephrogenic systemic fibrosis) may occur in the pediatric population as well. Lifetime exposure to radiation factors into the decision as well for the pediatric patient undergoing such imaging. Rare causes of hematuria in children include abdominal tumors (neuroblastoma and rhabdomyosarcoma), or arteriovenous malformations of the kidney vasculature. Red urine with negative dipstick can be encountered in neonates as a result of urate crystals excretion ("brick dust" urine), and at all ages as the result of medications (e.g., rifampin, phenazopyridine), foods such as beets, or aniline dyes.

Figures 64.1 and 64.2 give a reasonable approach to the evaluation of microscopic and gross hematuria, respectively.

PROTEINURIA

Quantitative assessment of proteinuria in children is affected by the unreliability of extended urine collections. However, its main purpose is to detect damage to the glomerular filter leading to increased permeability, and for this purpose the most sensitive parameter is the sieving coefficient (the relative concentration in glomerular filtrate and plasma water) of a molecule of a size that normally is just restrained by the glomerular filter. The urinary protein to urinary creatinine ratio provides a suitable approximation for use in clinical practice; being a ratio, it is independent of urine flow rate and can be estimated from a random urine sample. A value of less than 0.2 is considered normal and greater than 2.0 is considered nephrotic range proteinuria in children. The use of this ratio is preferred for children rather than the commonly performed 24-hour urine excretion for which more than 200 mg or 5 mg per kg per day usually is regarded as abnormal in children.

Normal urine contains a minimal amount of protein and is physiologic. Increased urine protein can be an isolated finding in a benign condition such as orthostatic proteinuria, or associated with significant kidney disease as nephrotic syndrome or CKD.

Definition

The urine dipstick is a sensitive screening tool for albuminuria and the presence of >1+ indicates a further diagnostic workup is prudent. A 24-hour urine collection is considered the gold standard method to quantify protein excretion, but is very difficult to achieve in children. When collected, values above indexed to body surface area (m^2). Values above 4 mg/m^2/h are pathologic. Values above 40 mg/m^2/h signify nephrotic range proteinuria. Because of the difficulty in performing the 24-hour urinary collection for protein, a random urine sample for protein (mg/dL) and creatinine (mg/dL) ratio (unitless), preferably on the first morning void, is commonly obtained. A ratio above 0.2, beyond the first year of life, is abnormal and warrants evaluation. Neonatal urine contains higher levels of albumin and lower molecular weight proteins, so an albumin/creatinine ratio is more commonly obtained.

History and Physical Exam

Febrile illness, strenuous exercise, and severe dehydration are commonly associated with transient proteinuria that has no long-term renal consequences. The presence of facial, periorbital, pedal, and/or scrotal edema are suggestive of low serum albumin and nephrotic syndrome. A thorough review of systems and a family history of kidney diseases are always important in the face of proteinuria.

Laboratory

The nature of the protein found in the patient's urine may imply the location of the renal lesion; glomerular diseases usually result in albuminuria whereas tubular pathology often leads to low molecular weight proteinuria such as beta-2-microglobulin. The finding of tubular proteinuria may be seen in the setting of generalized proximal tubular disorders that can also lead to aminoaciduria, phosphaturia, glucosuria, and/or bicarbonaturia (Fanconi syndrome). Low-molecular-weight proteinuria has also been linked to renal interstitial damage related to reflux nephropathy, obstructive nephropathy, or acute and chronic pyelonephritis. In orthostatic proteinuria the first morning urine protein to creatinine ratio is normal. In this condition a timed 24-hour urine collection will result in elevated protein excretion when the subject is upright with normal urine protein in recumbency. Nephrotic range proteinuria in the setting of peripheral edema, hypoalbuminemia, and hypercholesterolemia are diagnostic of nephrotic syndrome (see section on nephrotic syndrome for further evaluation). Many of the conditions leading to CKD are associated with proteinuria. In CKD, proteinuria itself is thought to be a perpetuating factor, leading to further damage by various mechanisms

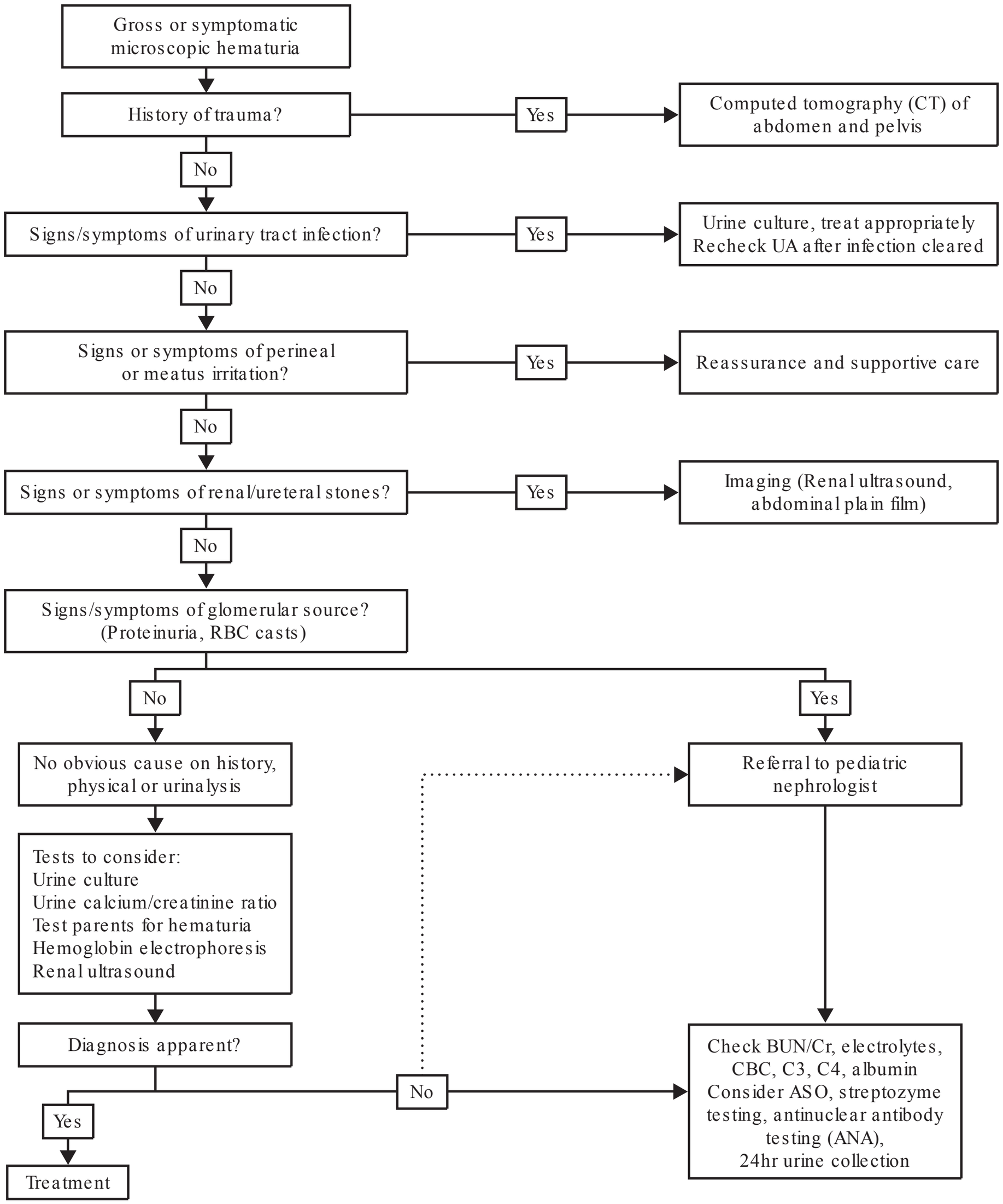

FIGURE 64.1 Approach to evaluation of gross hematuria.

including induction of apoptosis, cell atrophy, and epithelial to mesenchymal transformation. Isolated proteinuria in repeated urine samples over time is always an index of renal abnormality and should be further investigated. In addition to urinalysis, kidney function and serum electrolytes are required measurements in almost all cases of proteinuria. Persistent proteinuria of unclear etiology warrants the consideration of a kidney biopsy.

Table 64.5 lists a classification and some of the many causes of proteinuria in children.

ACUTE GLOMERULONEPHRITIS

The sudden onset of gross hematuria, proteinuria, azotemia, edema, and hypertension is a classic description of acute glomerulonephritis (AGN) in children and adolescents (Table 64.6). An important nodal point in the differential diagnosis is the level of serum complement factors, C3 and C4, which when depressed, suggest postinfectious (poststreptococcal disease most commonly) AGN, membranoproliferative GN, subacute bacterial endocarditis, shunt nephritis (plastic

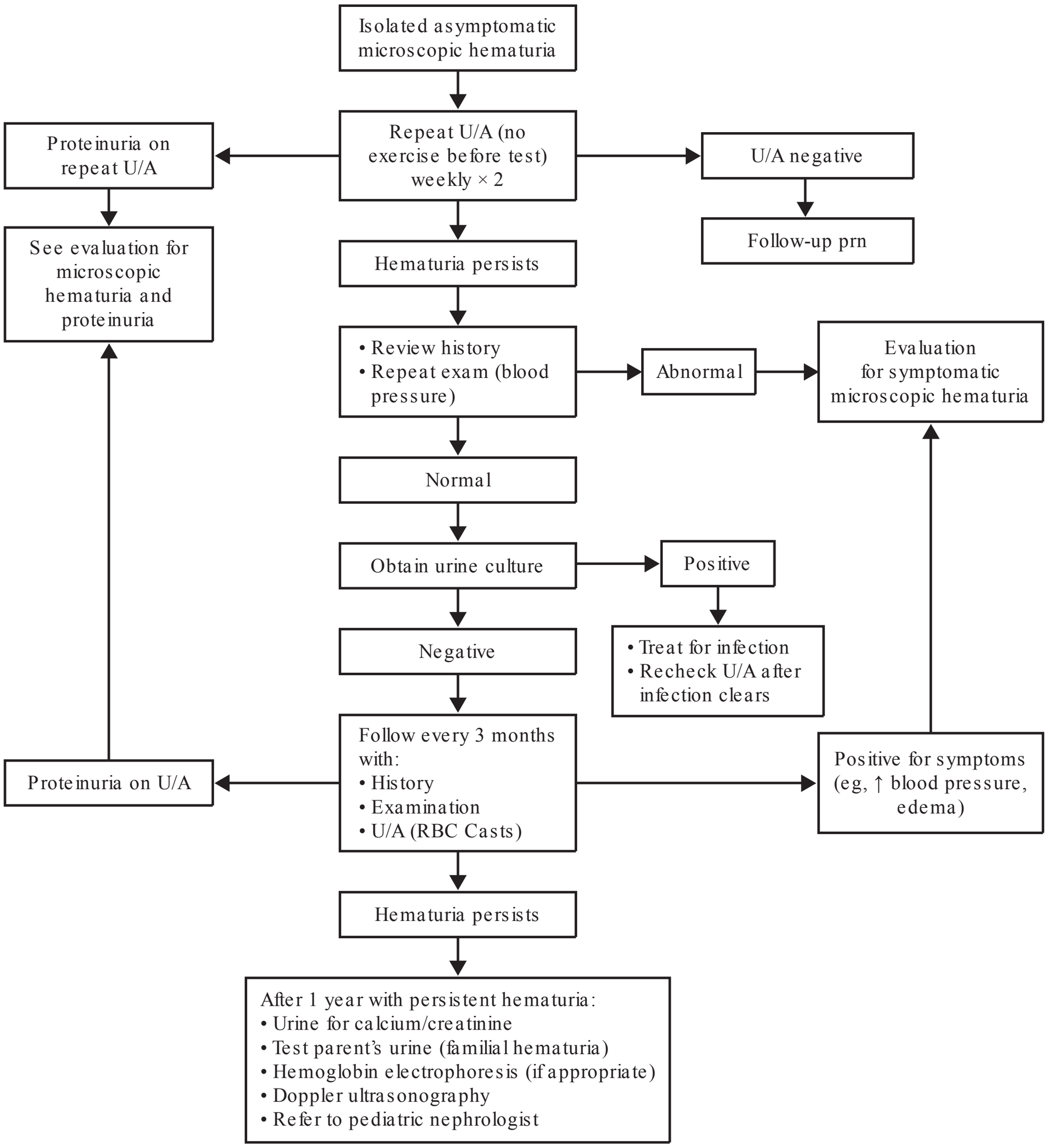

FIGURE 64.2 Approach to the evaluation of microscopic hematuria.

devices such as drains for cerebrospinal fluid placed into the vascular space), or, rarely, quartan malarial GN. Normocomplementemic postinfectious AGN, although occurring in up to 10% of those with biopsy-proven postinfectious AGN, suggests other etiologies that include IgA GN, Henoch-Schönlein purpura (when accompanied by a purpuric, lower extremity rash), vasculitides that include collagen-vascular diseases such as SLE, granulomatosis with polyangiitis (Wegeners), Goodpasture syndrome, or pauci-immune vasculitis.

Postinfectious AGN when associated with other components of thrombotic microangiopathies, including anemia, thrombocytopenia, and other wide-ranging organ dysfunctions, may connote diseases such as thrombotic thrombocytopenic purpura (TTP), shiga-toxin associated enterocolitis hemolytic uremic syndrome (STEC-HUS), or atypical HUS, a disease of complement regulatory protein mutational abnormalities, or in combination with autoantibodies to some of those proteins, in which the alternative complement pathway is constitutively activated and unregulated, leading to overactivity and resultant disease.

As in adults, a presentation with rapidly advancing kidney failure may be associated with a crescentic presentation on kidney biopsy that defines rapidly progressive glomerulonephritis (RPGN), most commonly associated in children with postinfectious AGN from postinfectious GN or one of the vasculitides noted.

64.5 Classification and Causes of Proteinuria in Children

Transient Proteinuria, associated with fever, vigorous exercise, volume depletion, or prolonged seizures

Orthostatic Proteinuria, in which the first morning urine is devoid of pathologic levels of protein but subsequent urines throughout the day reveal excess protein levels

Glomerular Proteinuria, arising from any form of infantile or childhood nephrotic syndrome, or as part of a glomerulonephritis of any etiology

Tubular Proteinuria, associated with primary or acquired diseases of the proximal tubule, obstructive uropathy, or tubulointerstitial nephritis (including pyelonephritis)

64.6 Common Causes of Acute Glomerulonephritis in Children and Adolescents

Associated with Hypocomplementemia	Associated with Normal Levels of Complement
Postinfectious AGN	GPA (granulomatosis with polyangiitis); MPA (microscopic polyangiitis); PAN (polyarteritis nodosa)
Collagen vascular disease (e.g., systemic lupus erythematosus)	Goodpasture
Membranoproliferative GN	IgA nephropathy
Shunt nephritis	Henoch-Schönlein purpura
Subacute bacterial endocarditis	Thrombotic thrombocytopenic purpura
Falciparum (quartan) malaria	STEC-HUS (commonly)
Atypical HUS (rarely)	Pauci-immune nephritis
STEC-HUS (rarely)	Atypical HUS (commonly) Alports syndrome

AGN, acute glomerulonephritis; GN, glomerulonephritis; HUS, hemolytic uremic syndrome; STEC, Shiga toxin-producing Escherichia coli.

Diagnostic evaluation of postinfectious AGN in children and adolescents should include evaluation for recent streptococcal infection of the throat (anti-streptolysin O titer), skin (anti-DNaseB titer), collagen-vascular disease, ANCA titers, complement levels, and a search for thrombotic microangiopathy (complete blood count [CBC], peripheral blood smear for schistocytes, reticulocyte count, platelet count, lactate dehydrogenase [LDH], haptoglobin level), and imaging of the kidneys by ultrasound to evaluate size and echo texture.

A percutaneous kidney biopsy in children and adolescents is a safe procedure performed by those with biopsy skills and the ability to provide proper anesthetic management. The biopsy is processed routinely for light, immunologic, and electron microscopic examinations and should be interpreted in collaboration with a pathologist skilled in pediatric kidney diseases.

As a general rule, the diagnosis of hypocomplementemic, postinfectious AGN in the child or adolescent does not mandate a kidney biopsy, as the hypocomplementemia resolves in 6 weeks in the overwhelming majority of cases, and the disease carries an excellent prognosis overall. Other causes of postinfectious AGN may indeed warrant a kidney biopsy early in its course for diagnostic, prognostic, and therapeutic decisions.

POSTINFECTIOUS GLOMERULONEPHRITIS[8]

From young childhood (older than three years) through late adolescence, the sudden appearance of gross hematuria with microscopic RBC casts, proteinuria, edema, and hypertension approximately 1 week to 1 month following a streptococcal pharyngitis or skin-based infection have defined the occurrence of postinfectious (poststreptococcal) postinfectious AGN. Documentation of a positive throat or skin culture for group A β-hemolytic streptococcus, or serologic evidence of elevated antistreptolysin O or DNaseB titers is commonly found and strengthens the diagnosis of postinfectious AGN. In developing areas of the world, many additional causative agents have been identified including other bacteria, viruses, fungi, and parasitic infectious agents.

The differential diagnosis of postinfectious AGN includes any kidney disease in which there is a nephritic picture, including IgA nephropathy, Henoch-Schönlein purpura, Goodpasture syndrome, systemic vasculitis related to ANCA, SLE, forms of hemolytic uremic syndrome, membranoproliferative glomerulonephritis, or an acute presentation of other chronic glomerular diseases.

Group A β-hemolytic streptococcus of the M-type is most commonly associated with the occurrence of postinfectious AGN, and type 12 is commonly isolated in cases of postinfectious AGN related to pharyngitis, and type 49 is commonly isolated in postinfectious AGN after skin-based infections. These are termed nephritogenic, although other types may produce postinfectious AGN too.

Postinfectious AGN is a prototypic hypocomplementemic disease in which there appears to be passive antigen-antibody complex deposition within the glomerulus in a characteristic subepithelial location, although many variants have been described that may mimic either membranoproliferative glomerulonephritis type I or, C3-glomerulopathy on kidney biopsy. The exact mechanisms whereby the circulating immune complexes deposit within the glomerulus remain uncertain, but may involve the alternative complement pathway (low C3, normal C4, and no C1q deposition in the kidney), rather than the classical complement pathway.

The hypocomplementemia is of short duration, with over 95% of patients recovering normal levels of complement C3 6 weeks after presentation. Postinfectious AGN may present with an RPGN clinical picture as well, with intense crescent formation found in the kidney biopsy. The depth of C3 depression does not correlate with disease severity or course. Up to 10% of patients with postinfectious AGN have normal C3 levels, depending on the time at which it is measured.

A kidney biopsy is rarely performed for postinfectious AGN related to group A β-hemolytic streptococcus, but is reserved for RPGN, uncertain assignment of postinfectious AGN as to etiology, or cases in which systemic manifestations suggest another cause of the postinfectious AGN.

More subtle cases of postinfectious AGN may be seen when the streptococcal disease is of a more epidemic nature, and in which gross hematuria is often absent and azotemia is minimal. We recommend a screening urinalysis of family members of index cases of postinfectious AGN, looking for hematuria and proteinuria, whether the case is epidemic or isolated.

No specific therapy has been shown to change the course of the typical child with postinfectious AGN, but we recommend looking for group A β-hemolytic streptococcus by culture, since treatment is warranted to prevent rheumatic fever if infection is present. The child with postinfectious AGN must be evaluated and managed for the potential complications of AGN that include malignant hypertension and its systemic sequelae, oligoanuria with hyperkalemia, dilutional hyponatremia, and acidosis. Rarely such management includes the use of iterative dialysis, unless a rapidly progressive picture is present and severe.

The prognosis of the overwhelming majority of isolated cases of postinfectious AGN that are related to an antecedent group A β-hemolytic streptococcal infection and without a picture of RPGN is uniformly excellent, with full recovery of normal kidney function and no long-term sequelae in over 95%. In developing countries, and in cases where prolonged dialysis is needed for RPGN, the prognosis is less well established, and continuation into ESRD or death may occur.

HENOCH-SCHÖNLEIN PURPURA GLOMERULONEPHRITIS[9]

The triadic finding of a predominant lower extremity and buttocks purpuric rash, abdominal pain, and fever in children and adolescents is prototypic for Henoch-Schönlein purpura (HSP). The disease is classified as a small vessel vasculitis of unknown etiology and, in addition to the organs involved above, may involve the kidney, the lower urinary tract, the joints, and, less commonly, the central nervous system or other organs. The disease is self-limited, may be recurrent, and the long-term morbidity is related to the degree, if any, of kidney involvement.

There is a literature that HSP is related to an antecedent infection, but no specific ones are implicated. Prior drug exposures have been noted rarely, and do not explain the overwhelming majority of such cases. Despite the presence of IgA deposition in the kidney, when kidney involvement is detected, circulating IgA levels are normal. Some evidence for circulating immune-complexes directed against altered moieties of IgA with subsequent mesangial deposition appears.

Kidney involvement is variable, and case series for frequency of involvement may reflect selection and referral biases. Even when initially absent as demonstrated by a normal urinalysis and serum creatinine initially, the kidney may become involved with a subsequent recurrence of the disease rash, but the exact frequency of such involvement subsequently ranges from infrequent to frequent for the biases cited. A good rule of thumb is that the absence of kidney involvement 2 months after clinical presentation of HSP (and without HSP recurrence) is generally associated with long-term sparing of kidney disease at all. Therefore, monitoring the child with HSP in those first 8 weeks after presentation with HSP, including a urinalysis, kidney function, and blood pressure measurement, seems warranted.

Kidney involvement, when present, ranges from low-grade proteinuria and hematuria, to AGN, or a nephrotic syndrome with heavy hematuria. A kidney biopsy is warranted for the latter three presentations for diagnosis, where a large range of findings may occur, from very little light microscopic abnormalities through focal and segmental proliferative GN and, at the worst, a crescentic GN. IgA is found commonly in association with IgG, C3, and fibrin in a granular, mesangial pattern that is indistinguishable from primary IgA nephropathy. HSP requires, therefore, the presence of the extrarenal system involvement as noted previously.

There is no specific treatment for HSP in general, and even the use of corticosteroids for the extrarenal manifestations remains unproven. In general, with general supportive measures the extrarenal disease improves and has no long-term sequelae in most.

In literature case series, the absence of kidney involvement 6 months after presentation is associated with a uniformly good outcome for normal kidney function. If severe manifestations of kidney involvement in HSP should occur the prognosis for good outcome diminishes, and should be followed for the appearance and/or management of CKD.

THROMBOTIC MICROANGIOPATHY[7]

Infants, children, and adolescents may present with a thrombotic microangiopathy (TMA) involving the kidney. TMA-based syndromes (Table 64.7) are microvascular occlusive disorders that result from aggregation of platelets, thrombocytopenia, and mechanical injury to erythrocytes, ultimately leading to organ dysfunction. A more specific definition of TMA is the activation of the endothelium due to various insults followed by a cascade of pathologic responses, including among others, platelet and/or complement activation of the terminal (C5b-9) complex, microthrombi formation, thrombocytopenia, and microangiopathic hemolytic anemia. Atypical hemolytic uremic syndrome (HUS) occurs both in the pediatric and adult populations; severe kidney impairment is a prominent but not an essential feature of the disease.

The most common cause of TMA and HUS is that associated with shiga-toxin producing infections (now termed STEC-HUS), including Escherichia coli serotype 0157:H7 and Shigella dysenteriae serotype 1, accounting for more than 90% of HUS cases. Recently, an outbreak in adults was linked to a unique serotype of E. coli, O4:H4. New evidence points to complement activation in STEC-HUS. The term atypical HUS has been used to describe cases of TMA not caused by shiga-toxin associated microorganisms and bacterial infections in general, and in which thrombotic thrombocytopenic purpura (TTP) has been excluded in the differential diagnosis by demonstrating levels of ADAMTS13 activity above 5% to 10%.

Atypical hemolytic uremic syndrome is a rare, life-threatening, chronic, genetic disease of uncontrolled alternative pathway complement activation. The understanding of the pathophysiology and genetics of this disease has expanded over recent decades and promising new developments in the management of atypical HUS have emerged.

In 50% to 60% of cases of atypical HUS, a genetic mutation in complement regulatory proteins and/or autoantibodies against these proteins has been found as an explanation for constitutive complement activation. Mutations have been described in complement factor H (CFH), complement factor I (CFI), Membrane Cofactor Protein (MCP), complement factor B (CFB), myosin binding protein C3 gene (C3), and thrombomodulin. In addition, autoantibodies to CFH can cause atypical HUS and are commonly associated with deletions of complement factor H-related proteins CFHR1 and CFHR3. Mutations in either CFH, CFI, MCP, thrombomodulin, and/or CFHR1/3 with autoantibodies to CFH are associated with loss of regulatory control of the alternative pathway of the complement cascade. Mutations in CFB and C3 are gain of function mutations leading to complement over-activation. A very rare cause of atypical HUS is genetic deficiency of cobalamimase activity.

However, this leaves another 40% to 50% of patients in whom a mutation or autoantibody cannot be demonstrated but for whom atypical HUS is the diagnosis. Thus, the ultimate diagnosis of atypical HUS does not require a formal demonstration of its underlying genetic cause. Less than 20% of atypical HUS cases are familial, with both autosomal-dominant and autosomal-recessive inheritance reported. Autosomal-recessive cases tend to present in childhood whereas autosomal-dominant cases more typically present in adulthood—prognosis is poor regardless of inheritance. Identification of a genetic mutation, although not required for an individual's diagnosis or management of atypical HUS, may be helpful for identifying and monitoring disease carriers and for providing genetic counseling.

Loss of function mutations in CFH are most common and have the worst prognosis based on registry data, with 60% to 70% of patients progressing to end-stage renal disease (ESRD) or death within a year of disease onset. The ultimate kidney and patient-based prognoses for patients with CFI mutations appears slightly better, followed by patients with MCP mutations, of whom 20% require renal replacement therapy. Patients without demonstrated mutations have similar dire outcomes, however, raising the idea that the presence or absence of a given mutation may have limited prognostic value, except for the MCP mutation that may not recur after kidney transplantation.

64.7 TMA-Based Diseases

- Thrombotic thrombocytopenic purpura
  - Congenital ADAMTS13 deficiency
  - Antibody-mediated ADAMTS12 deficiency
- Hemolytic uremic syndrome
  - STEC-HUS
  - Pneumococcal HUS
  - Atypical HUS (atypical HUS)
- TMA associated with
  - Medications
  - Hypertension
  - Pregnancy/HELLP syndrome
  - Solid organ transplantation
  - Stem cell transplantation
  - Malignant solid tumors
  - HIV
  - Vasculitis, such as systemic lupus erythematosus

TMA, thrombotic microangiopathy; HUS, hemolytic uremic syndrome; STEC, Shiga toxin-producing Escherichia coli; HELLP: hemolysis, elevated liver enzymes, low platelet count

Until recently, there have been no specific therapies for atypical HUS. Therapeutic plasma exchange or plasma infusion has generally been the initial approach to disease management, although there are no randomized controlled trials of plasma therapy in atypical HUS to establish its effectiveness. Plasma exchange may only be beneficial for atypical HUS in the short term, because long-term kidney outcomes are uniformly poor with a varying short-term response in hematologic parameters. Plasma exchange would not be expected to be effective for patients with mutations in MCP, a transmembrane protein. Patients who do respond to plasma exchange frequently become plasma dependent, requiring long-term therapy to maintain remission.

Kidney transplantation can be successful for patients with MCP mutations. MCP is cell membrane-bound and highly expressed in the kidney; kidney transplant, then, would be expected to halt the disease process. Other mutations or unknown ones have led to high relapse rates of atypical HUS in the transplanted kidney. CFH and CFI mutations have been studied more extensively. These circulating proteins are primarily synthesized in the liver. Not unexpectedly, atypical HUS recurs in 80% of patients with CFH mutations and 90% of patients with CFI mutations after an isolated kidney transplant. Living-donor kidney transplantation is contraindicated in patients with atypical HUS due to mutations in CFH, CFI, C3, and CFB without other therapies concomitantly.

Combined liver-kidney transplantation has been attempted for patients with CFH and CFI mutations to address the abnormal protein synthesis in the liver and its downstream effect on the kidney. Simultaneous liver-kidney transplantation with prophylactic use of plasma therapy has been successful in patients with CFH mutations. However, liver-kidney transplantation is associated with a higher mortality rate than kidney transplantation alone. In the absence of a noted mutation, comprising a sizable fraction of patients with atypical HUS, liver-kidney transplantation should be avoided.

A pathophysiologic-based treatment in atypical HUS is available now with eculizumab, through inhibiting the formation of the common terminal complement complex (C5b-9). Its recent approval for atypical HUS in adults and in children represents its first approved use for pediatric patients. Due to the impaired capacity for opsonization and clearance of encapsulated organisms, meningococcal disease is a risk with the use of eculizumab and has been reported among patients given eculizumab for paroxysmal nocturnal hemoglobinuria (PNH). Patients must receive the meningococcal vaccine prior to treatment initiation.

NEPHROTIC SYNDROME IN THE FIRST YEAR OF LIFE[4,5]

The classic triad of findings in nephrotic syndrome in children, adolescents, and adults—hypoalbuminemia, high-degree proteinuria, and edema—are found in infants with nephrotic syndrome too. Congenital nephrotic syndrome has been used to describe the disease in utero through the first 3 months of life, whereas infantile nephrotic syndrome has referred to the development of the disease in months 4 through 12. We find this an arbitrary division, as there is great overlap in the causes between the two groupings, and prefer nephrotic syndrome in the first year of life (NSFL).

The differential diagnosis of NSFL includes disease secondary to congenital maternal infections (e.g., syphilis, cytomegalovirus) or from genetic causes. The majority of the genetic causes involve mutations in kidney morphogens such as WT-1, or mutations in genes related to the integrity of the tri-partite glomerular filtration barrier (the podocyte foot processes, the fenestrated glomerular endothelium, and the glomerular basement membrane). After exclusion of infection-related NSFL, NSFL is now considered a monogenic disease, with one of four genetic mutations (nephrin, podocin, WT1, LAMB2) accounting for over 66% of the cases in a recent Western European series. The disease is not responsive to corticosteroids or immunosuppressive medications as a general principle. Prompt referral to a center skilled in management of infantile nephrosis is recommended.

NSFL may be seen in syndromic diseases of newborns as well, and the clinician should evaluate the patient for extrakidney malformations including disorders of sexual differentiation (see below). For a comprehensive listing, the reader can access: http://www.ncbi.nlm.nih.gov/omim?term=nephrotic%20syndrome%20in%20infancy.

NEPHROTIC SYNDROME IN CHILDHOOD[6]

Primary nephrotic syndrome in children from 15 months through 8 to 10 years of age includes minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN; types I, II, III), and membranous nephropathy (MN). The overwhelming majority of children will have MCNS when the patient has normal kidney filtering function, is nonazotemic, normotensive, and with normocomplementemic. To date, the initial response to a course of oral corticosteroids, 2 mg/kg/day or 60 mg/m^2 BSA/day, defines the disease as steroid-responsive or resistant. Initial corticosteroid resistance mandates a biopsy for histologic diagnosis.

Steroid responsiveness is further delineated by frequency of relapse, into no further episodes (~10%–15% of cases) or recurrent (relapse) nephrotic syndrome, which is either infrequent (less than three times in 1 year) or frequent (three or more relapses per year). Treatment algorithms have evolved for relapsing disease. Frequently relapsing corticosteroid responsive disease may become corticosteroid-resistant as well, and treatment algorithms have evolved for these cases too. Kidney biopsy is indicated for corticosteroid resistance, and often when contemplating institution of

potent immunosuppressive therapy with or without corticosteroids for the frequently relapsing course.

Genetic mutations in the components of the glomerular filtration barrier are increasingly recognized as a cause of FSGS in childhood nephrotic syndrome, and other such mutations can be expected. Additionally, mutations in many other genes have been linked to corticosteroid-resistant nephrotic syndrome as well, either occurring alone or as part of other diseases. A listing to date can be accessed at: http://www.ncbi.nlm.nih.gov/omim?term=Genetic%20causes%20of%20nephrotic%20syndrome.

Mutations in regulatory proteins of the alternative complement pathway involved in innate immunity have been linked to childhood MPGN, especially type II (dense deposit disease) or a recently described C3 nephropathy. Membranous nephropathy has been linked to the M-type phospholipase A(2) receptor (PLA(2)R) as a candidate antigen in 70% of cases of idiopathic membranous nephropathy. Recently, the presence of cationic bovine albumin, or circulating antibodies to it, was demonstrated in the serum of other children with idiopathic MN.

So-called secondary causes of nephrotic syndrome in this age grouping are much less common than in the adolescent patient, but may include the emergence of nephrotic syndrome in collagen vascular diseases represented by SLE; in infections represented by hepatitis B, HIV, or quartan malaria; from effects of drugs, represented by chemotherapy agents used for treatment of childhood malignancy or immunosuppressive drugs represented by sirolimus; or in systemic metabolic diseases represented by Fabry disease. A careful history and physical examination generally brings secondary causes to light in this age grouping.

NEPHROTIC SYNDROME IN ADOLESCENTS

The frequency of MCNS in children older than 10 years and in adolescents drops dramatically when compared to the younger age group described previously, and the other primary forms therefore assume a greater importance in the differential diagnosis. The emergence of the more usual causes of adult-onset nephrotic syndrome is common in the differential diagnosis as well (e.g., malignancy associated nephrotic syndrome), with the exception of the nodular sclerosis of advanced type 1 diabetes mellitus unless the disease has been present for >10 years in the adolescent patient. Almost uniformly, a kidney biopsy is performed for accurate diagnosis in the adolescent patient with nephrotic syndrome.

METABOLIC ACIDOSIS[10,11]

Definition

Chronic metabolic acidosis is defined by the presence of a reduced blood [HCO_3^-] as well as a reduced pCO_2 level resulting from compensatory hyperventilation. Importantly, there is developmental regulation of bicarbonate handling by the kidney. The normal range for serum bicarbonate is lower for preterm infants (16 to 20 mmol per L) and full-term infants (19 to 21 mEq per L) than for children and adults (24 to 28 mmol per L). This is explained by both the inability to excrete the byproducts of growth and metabolism on the one hand in infants, and the higher level of endogenous acid generated by protein metabolism and bone growth in the infant when compared to the older child or adolescent.

Additionally, the lowered bicarbonate concentration in preterm and term infants, compared to older children and adolescents, reflects the reduced bicarbonate threshold of nephron heterogeneity and a reduced fractional bicarbonate resorption, perhaps related to an expanded extracellular water volume in infants.

Postnatal maturation of the proximal tubular capacity for bicarbonate resorption results from increases in activities of the sodium-hydrogen exchanger (NHE) and H+-ATPase. Low carbonic anhydrase activity further exacerbates the limited bicarbonate resorption.

Developmentally, the capacity to respond to acid loading increases with advancing gestational and postnatal ages. In response to acid loading with ammonium chloride, urinary pH values of less than 6 are rarely observed in premature infants until the second month of life. In contrast, by the end of the second postnatal week, term infants can generate minimal urinary pH values of 5.0 or lower, comparable to those in the adult. The immaturity of the collecting duct intercalated cells may further lessen the ability of the neonatal kidney to eliminate an acid load.

Secondary to the developmental changes noted, up to 10% of preterm infants develop a hyperchloremic metabolic acidosis during weeks 1 to 3 of life, and this has been termed "late metabolic acidosis of infancy," despite an otherwise healthy appearance but with subnormal weight gains. Typically, spontaneous remission occurs in the subsequent 2 weeks.

History and Physical Examination

Chronic metabolic acidosis uniformly affects somatic growth in a negative way, with reduced body mass and linear height. Additionally, anorexia, nausea, emesis, and diarrhea are not uncommon gastrointestinal manifestations of a kidney disease–mediated metabolic acidosis. Apathy, listlessness, and reduced activity may be ascertained as well.

Patients generally have reduced growth parameters, especially when followed longitudinally with prior values. Patients with chronic metabolic acidosis may have a pallor, reduced skin perfusion, and, if from a primary disorder of organic acid metabolism, hepatomegaly. CKD and its attendant acidosis from obstructive uropathies may produce an abdominal mass (kidney). Chronic metabolic acidosis impairs normal bone mineralization, so the presence of rickets should be sought for as well (see Rickets, later). Rarer disorders of adrenal hormone metabolism produce incomplete

masculinization of genotypic males and masculinization of genotypic females.

Laboratory

As in the adult with chronic metabolic acidosis, the serum anion gap should be measured, remembering that until later childhood, normal values for the calculation are 12 to 15 mEq per L, and decreasing to 10 to 12 mEq per L thereafter. An elevated serum anion gap metabolic acidosis has an expanded differential in infants and children, as it includes inborn errors of metabolism of organic acids and amino acids; an increased likelihood of poisoning with salicylates, methanol, or ethylene glycol; lactic acidosis; diabetic ketoacidosis; as well as hypermetabolic states such as leukemias or solid tumors. In younger children, acute and chronic kidney failure may result in an elevated anion gap metabolic acidosis too.

Anormal anion gap metabolic acidosis demands measurement of the urinary anion gap (the sum of [Na + K] − Cl). Metabolic acidosis associated with a negative urinary anion gap implies an intact distal tubule acidification process, and may be seen with intestinal bicarbonate losses, proximal renal tubular acidosis (RTA, type II), the use of acetazolamide (often used to reduce cerebral spinal fluid production in infants and children), or, very rarely, exogenous acid administration.

Metabolic acidosis associated with a positive urinary anion gap demands measurement of the urinary pH by a pH meter-based method. When the measured urinary pH is >5.8, distal renal tubular acidosis (RTA) is present, as either type I (hypokalemia) or type IV (hyperkalemia). The latter may be seen with obstructive uropathy in infants and children. When the urinary pH is measured at ≤5.8, a type IV RTA is present, and the plasma renin activity (PRA) should be measured. When the PRA is elevated, the plasma aldosterone level should be determined, and if high, either pseudohypoaldosteronism type I (genetic, occurring in a kidney-limited, autosomal-dominant form due to mutations in the mineralocorticoid receptor, or as a widely disseminated, multiple organ form causing widespread aldosterone resistance due to one of several mutations in the subunits of the epithelial Na-channel) or type III (observed in infants and children with obstructive uropathy, acute pyelonephritis, or bilateral vesicoureteral reflux) diagnosed. Alternatively, when the PRA is elevated but the plasma aldosterone is reduced, a plasma cortisol must be determined. When that cortisol is normal and shows circadian rhythmicity, primary hypoaldosteronism is defined, and when that cortisol is low and shows the absence of circadian rhythmicity, concern over congenital adrenal hyperplasia (look also for disorders of sexual differentiation) or Addison disease may be present.

In this diagnostic pathway, if the PRA is reduced, and the patient is hypertensive, Gordon syndrome (chloride shunt) should be considered, whereas if the blood pressure is normal, conventional causes of hyporeninemic hypoaldosteronism seen in adults can be considered for children and adolescents too. Such disorders are associated with mutations of the WNK1 and WNK4 protein kinases.

64.8 Elevated Anion Gap

Category of Acidosis	Specific Clinical States or Diseases
Lactic acidosis	Hypoperfusion Mitochondrial myopathies Inborn errors of carbohydrate metabolism
Ketoacidosis	Diabetic ketoacidosis
Organic acidemias	
Fatty acid oxidation defects	
Ingestions	Methanol, ethanol, ethylene glycol, salicylate intoxication
Advanced end-stage renal disease	
Rhabdomyolysis	
Normal Anion Gap (Hyperchloremic) Acidosis	
Loss of bicarbonate	
Loss through the gastrointestinal tract	Diarrhea, laxative abuse, enteric fistulae, ureteral-sigmoid connections
Kidney loss	Proximal (type 2) RTA
Reduced hydrogen secretion	Distal (type 1) RTA Type 3 RTA
Early end-stage renal disease	

RTA, renal tubular acidosis.

Some of the general causes of chronic metabolic acidosis are listed in Table 64.8.

RENAL FANCONI SYNDROME

The term refers to a complex and generalized proximal tubulopathy that has many different etiologies. In its complete form, there is a generalized disorder of brush border transport mechanisms leading to excessive loss of water (urine osmolality ≤300 mOsm per kg H_2O), salt wasting (fractional sodium excretion >1%), potassium wasting (TTKG >12), bicarbonaturia (FE >15%), phosphate (TRP

below 85%), amino acids, glucose, and uric acid into the final urine—such that a chronic metabolic acidosis with hyponatremia, hypokalemia, hypophosphatemia, and reduced serum uric acid level, often in concert with volume depletion, occurs. Almost all causes of a renal Fanconi syndrome have excessive tubular proteinuria (e.g., increased excretions of B2-microglobulin, retinol-binding protein). Additionally, reduced production of the active vitamin D metabolite may occur as well, leading in concert with the other parts of the disorder to rickets and secondary hyperparathyroidism. Hypercalciuria is an inconsistent finding in all forms of renal Fanconi syndrome.

Partial forms of the renal Fanconi syndrome have been described in some diseases, such as those associated with mutations in the CLCN5 or OCRL-1 gene that goes by several names (Dents syndrome 1, hereditary X-linked nephrolithiasis with renal failure, Dents syndrome-2, respectively.), or in hereditary hypercalciuria with hypophosphatemia (HHRH) due to Npt2 gene mutations, or severe nutrient vitamin D deficiency.

A renal Fanconi syndrome must be distinguished from single molecule transport disorders of the proximal tubule such as in patients with X-linked dominant hypophosphatemic rickets, autosomal-dominant hypophosphatemic rickets, cystinuria (the generalized dibasic aminoaciduria is only clinically relevant due to the insolubility of cystine in normal urine), isolated renal glycosuria, lysinuric protein intolerance (a cause of hypoglycemia in young children), or proximal bicarbonate loss in isolated proximal renal tubular acidosis.

Fanconi syndrome from inherited causes generally produces growth failure and often, rickets. Inherited causes of renal Fanconi syndrome include cystinosis (mutation in cystinosin), Dents disease (CLCN5 or OCRL mutation), Lowe oculocerebrorenal syndrome (OCRL mutation, Fanconi Bickel glycogenosis [Glut2 mutation]), tyrosinemia, Wilson disease, hereditary fructose intolerance, mitochondrial myopathies of diverse nature, galactosemia, or in an idiopathic form.

Acquired forms of renal Fanconi syndrome in children may result from toxic effects of therapeutic agents such as chemotherapy (ifosfamide, cisplatin), valproic acid, or aminoglycosides, or result from poisonings from heavy metals (lead, mercury, cadmium, uranium) or from glue sniffing, use of paraquat, or as a result of tubular injury associated with kidney transplantation.

CYSTINOSIS[12–14]

Cystinosis is the most common cause of an inherited Fanconi syndrome in children. It is an autosomal-recessive disease characterized by the abnormal accumulation of the amino acid cystine in lysosomes of all tissues due to a defective cystine transporter protein, cystinosin. The gene responsible for nephropathic cystinosis, CTNS on chromosome 17p, encodes for a 367-amino acid transmembrane protein called cystinosin. A common major deletion underlies most affected patients in Europe; other mutations have been reported.

Typically, cystinosis is a multisystem disease causing failure to thrive, recurrent volume depletion, polyuria and polydipsia, vomiting, constipation, Fanconi syndrome, and CKD in infancy or early childhood. Affected children may be erroneously diagnosed with nephrogenic diabetes insipidus or diabetes mellitus due to polyuria and recurrent episodes of volume depletion. Chronic metabolic acidosis contributes to failure to thrive. Phosphaturia can result in a form of hypophosphatemic rickets.

The hallmark of nephropathic cystinosis is the accumulation of cystine in nearly all tissues, including kidneys. Corneal accumulation of cystine crystals leads to photophobia beginning in mid-childhood. Crystal storage in the thyroid causes hypothyroidism at an average age of 10 years. Feeding dysfunction including reflux, dysmotility, and swallowing abnormalities is common, further contributing to impaired growth in this condition. Limited and specific cognitive dysfunction with impaired visual and spatial abilities is common, even in heterozygous siblings who do not manifest other features of the disease. The eGFR is only mildly impaired in infancy and early childhood. However, untreated, the disease progresses to chronic interstitial disease and glomerular necrosis with ESRD occurring at a median age of 9.2 years in untreated patients.

The diagnosis is made by measurement of an elevated leukocyte cystine content. Prenatal diagnosis is available through testing of amniotic fluid or chorionic villus samples. Supportive treatment includes replacement of tubular fluid and solute losses, and affected patients require increased water intake as well as supplementation with sodium-potassium citrate or sodium bicarbonate, sodium phosphate, 1,25-dihydroxyvitamin D., and possibly L-carnitine. Close attention to growth and nutritional needs is critical from an early age, and many centers now recommend placement of a gastrostomy tube in infancy to ensure adequate nutritional intake and compliance with the multiple required medications. Hypothyroidism should be treated appropriately. Although the linear growth failure in cystinosis is not associated with growth hormone deficiency, the administration of recombinant growth hormone to affected children has been shown to be of benefit.

Specific treatment involves depletion of intralysosomal cystine with cysteamine bitartrate, administered every 6 hours around the clock for the life of the patient, to form mixed disulfides that are capable of being transported out of the lysosome. Such treatment has been shown to slow the progression of renal insufficiency and thyroid disease in this condition. Specifically, chronic cysteamine therapy has shifted the point at which serum creatinine reaches 10 mg per dL from around 10 to 23 years of age. The search for newer agents that deplete intracellular accumulation of cystine but with a reduced frequency of administration is sought. Corneal crystal accumulation does not respond to oral cysteamine but instead requires topical treatment.

Patients with renal failure are candidates for peritoneal dialysis, hemodialysis, or renal transplantation. Cystine accumulates in renal allografts but does not cause functional abnormalities. It has been suggested that posttransplantation diabetes mellitus occurs at increased frequency in patients with cystinosis. Ongoing cysteamine treatment posttransplantation is indicated to prevent other systemic manifestations of this disease. With improved survival due to advancements in renal replacement therapy, it has become apparent that cystinosis is associated with severe neurologic sequelae, including cerebral atrophy, pyramidal signs, difficulties with speech, cerebellar ataxia, and pseudobulbar palsy. Further studies are needed to determine whether such neurologic deficits can be prevented with lifelong cysteamine-based therapies.

METABOLIC ALKALOSIS[15–18]

Definition

Metabolic alkalosis is characterized by an elevated serum bicarbonate level, in association with an elevated pCO_2 level as a compensatory change.

History and Physical Examination

Growth parameters should be determined, as well as the pattern of growth historically. Feeding disturbances are not uncommon, and stool and urinary outputs can be ascertained historically. The presence of edema may be sought, and determination of the state of volume repletion from the usual findings on examination should be made.

Laboratory

The major differential in determining the etiology of a chronic metabolic alkalosis must include the urinary chloride level, which when low (≤20 mEq per L) defines an extra-kidney generation of the metabolic alkalosis, or when high (>20 mEq per L) defines a kidney-generated metabolic alkalosis.

Extra-kidney generated metabolic alkalosis includes some diarrheal states, low chloride intake from improperly made infant formulas, loss of gastric fluid such as with emesis, prolonged nasogastric suction, or congenital pyloric stenosis, cystic fibrosis, or a rare congenital chloride diarrhea or villous colonic adenoma. Hypoparathyroidism has been associated with this form of metabolic alkalosis, as have other rare conditions such as glucose infusions after starvation and inappropriate alkali administration.

Kidney-generated metabolic alkalosis demands an evaluation of the blood pressure of the patient, and when high, further determination of the plasma renin activity (PRA). A high PRA is seen in cases of renal artery stenosis from any cause, often bilateral, or in rare cases, renin-secreting tumors. When PRA is low, plasma aldosterone levels must be evaluated. When elevated, consideration for glucocorticoid-remediable hypertension (genetic mutational condition in which aldosterone comes under control of ACTH) or, less commonly, primary hyperaldosteronism should be entertained. When the plasma aldosterone is reduced, syndromes including Liddle syndrome, apparent mineralocorticoid excess (AME), 11α-hydroxylase deficiency, and true licorice ingestion should be entertained.

In kidney-generated metabolic alkalosis in which the blood pressure is normal, and the use of loop diuretics has been eliminated by history, hereditary potassium-losing tubulopathies such as Bartter syndrome (associated with hypercalciuria) or Gitelman syndrome (associated with hypocalciuria) should be entertained.

DISORDERS OF SODIUM HOMEOSTASIS

History and Physical Examination

Central to understanding the mechanism of disorders of serum sodium (Na) in either direction is the determination of the patient's intravascular volume status, ranging from reduced, normal, or increased, by conventional means of weights, and signs and symptoms well known to clinicians including skin turgor, the presence of tears, the moistness of the mucous membranes, the presence of orthostatic blood pressure changes, resting tachycardia, and alterations of skin perfusion/capillary refill time.

Laboratory

A complete picture of the blood electrolytes, blood osmolality, and kidney function should be obtained initially, and monitored at frequent intervals to assure patient safety. If at all possible, relatively simultaneous determinations of urinary Na, potassium (K), and chloride (Cl) excretions, the creatinine and urea nitrogen, and the urinary osmolality, should be obtained in the diagnostic evaluation of the disorder.

Hypernatremia

Algorithms for evaluation of hypernatremia (serum Na ≥150 mEq per L) based on the intravascular volume status of the patient and the urinary Na response have been published extensively for adults and do not need much additional comments when applied to children and adolescents. However, it should be remembered that very premature infants in the first weeks to months of life often lose substantial water through their exposed skin, producing hypernatremia, and infants and children with various causes of renal dysplasia or hypoplasia may have substantial natriuresis, leading to hypernatremia in the very young. Diarrheal diseases alone are likely the most common cause of hypernatremic volume depletion in infants and young children, and are ascertained easily with a careful history. An important point to remember is that the very premature infant can generate a urinary osmolality only about 20% of the maximal one in the adolescent and adult, or about 200 mOsm per kg H_2O.

Chronic disorders of water metabolism (outside of the first month of life and especially in premature infants, as disturbances in this time frame may represent immature kidney development alone) may result in hypernatremia and hypoosmotic urine, including central or nephrogenic diabetes insipidus. The differentiation of these disorders requires a formal water deprivation test under most circumstances, and must be performed in infants and children in the inpatient setting. The reader is encouraged to obtain consultation with a pediatric nephrologist or endocrinologist before studying water metabolism in this population. Normative data for interpretation of the various portions of the water deprivation test have been established.

Hyponatremia

Algorithms for evaluation of hyponatremia (serum Na ≤130 mEq per L) based on the intravascular volume status of the patient and the urinary Na response have been published extensively for adults and do not need much additional comment when applied to children and adolescents. Some hyponatremic diseases more unique to pediatrics include hypovolemic urinary salt conservation in cystic fibrosis and pancreatitis (from congenital malformations), whereas the hypovolemic urinary salt loss diseases more unique to pediatrics include genetic salt-losing nephropathies (Bartter syndrome, Gitelman syndrome, pseudohypoaldosteronism, salt-losing forms of congenital adrenal hyperplasia, and adrenoleukodystrophy). A not uncommon form of euvolemic hyponatremia associated with Na conservation by the kidney is the use of an inappropriately mixed infant powdered formula (excess water intake producing dilutional hyponatremia).

DISORDERS OF POTASSIUM HOMEOSTASIS

Hypokalemia

By definition, hypokalemia is present when the plasma K is <3.5 mEq per L in a patient. The urinary K response to hypokalemia is critical for the differential diagnosis. Potassium conservation (urinary [K] <20 mEq per L) is commonly seen when the dietary potassium intake is normal, but there are excessive extra-renal losses in the gastrointestinal (GI) tract, skin, or from increased intracellular localization of potassium. Rarely, prolonged parenteral fluid administration in the absence of potassium may be the reason for hypokalemia, but should be obvious from inspection of the hospital record.

GI losses may be associated with concomitant acidosis (diarrhea, malabsorption syndromes, intestinal or biliary fistulae, enterostomy losses, or the presence of an ureterosigmoidostomy), or with concomitant alkalosis (gastric drainage, pyloric stenosis, emesis, congenital chloride diarrhea), or variable acid-base abnormalities, such as with laxative or enema abuse or a villous adenoma. Cutaneous losses may be seen in cystic fibrosis or burn states. In hospitalized patients, hypokalemia is most commonly observed in children from altered intracellular distribution, including administration of insulin or beta-sympathomimetic medications. At all ages, consideration for the genetic disease, familial hypokalemic periodic paralysis, should be entertained.

When the hypokalemic patient has a urinary K >20 mEq per L, the response of the blood pressure allows an accurate differential diagnosis. When the blood pressure is normal or reduced, as in Fanconi syndrome, Bartter syndrome, or Gitelman syndrome, the use of diuretics or a postobstructive diuresis may be considered.

In the kaluretic hypokalemic patient with a high blood pressure, the plasma renin activity (PRA) should be determined, and if high, renovascular disease or rarely, a renin-secreting tumor should be entertained. In the patient with a low PRA, the plasma aldosterone must be measured to proceed with the differential diagnosis. When reduced or normal, diseases such as Liddle syndrome, AME, true licorice ingestion, or glucocorticoid or mineralocorticoid administration should be entertained. When the plasma aldosterone level is high, glucocorticoid remediable hypertension or rarely in children, primary hyperaldosteronism, should be entertained.

Hyperkalemia

By definition hyperkalemia is present when the plasma K is >5.5 mEq per L in a patient. It is important to remember that a markedly elevated platelet or white blood cell count may lead to test tube hemolysis and hyperkalemia that is not present in the patient (pseudohyperkalemia). The urinary K response to hypokalemia is critical for the differential diagnosis.

When the urinary K >20 mEq per L, the clinician should look for sources of exogenous potassium administration, such as from the diet or from blood transfusions in patients with reduced GFR (a unit of blood has <4 mEq of K). Without an identified exogenous source of potassium, altered K distribution (reduced intracellular localization) and hyperkalemia may result from chronic metabolic acidosis, insulin deficiency, familial hyperkalemic periodic paralysis, hyperthyroidism, or from specific drugs such as beta-blockers, succinylcholine, or digoxin overdosage.

When the urinary K is ≥20 mEq per L, and the GFR is reduced, generally to below 30 mL/min/1.73 m^2 body surface area, acute kidney injury (AKI) or CKD may be the culprit. In the absence of a reduced GFR to such levels, the plasma aldosterone helps provide a critical differential point. Elevated plasma aldosterone levels define pseudohypoaldosteronism types I and III (see above). Normal plasma aldosterone levels define defective kidney secretion of potassium, as in sickle cell disease, SLE, or type IV RTA associated with obstructive uropathy, or the effects of drugs which include spironolactone, triamterene, amiloride, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcineurin inhibitors, nonsteroidal anti-inflammatory agents, or trimethoprim. Low plasma aldosterone levels require measurement of the

plasma renin activity, which when high suggest congenital adrenal hyperplasia, causes of adrenal failure, or rarely, specific defects in aldosterone biosynthesis (CMO 1 or 3), and when plasma renin activity is reduced, suggest Gordon syndrome (PHA type 2) or other causes of hyporeninemic hypoaldosteronism.

DISORDERS OF CALCIUM, PHOSPHORUS, AND MAGNESIUM

Disorders of Calcium

Hypocalcemia[19,20]

Definition

When the serum albumin is normal, hypocalcemia is defined as a decrease in serum total calcium to <8.3 mg per dL, or as a decrease in blood ionized calcium <4.4 mg per dL. Formulas for correction of serum total calcium based on a reduced blood albumin have not been validated in infants and children, but likely apply to adolescents.

History and Physical Examination

Clinical symptoms of hypocalcemia are protean and include altered neuromuscular function (tetany, generalized or focal seizures), altered sensorium and psychological disturbances, intracranial calcium deposits, bradyarrthymias, cataracts, constipation, dental enamel hypoplasia, neurodermatosis, and alopecia, among others.

Laboratory

Classification of hypocalcemia is best done by evaluation of a simultaneous serum phosphorus and level of alkaline phosphatase activity. If serum phosphorus is reduced, and the activity of alkaline phosphatase elevated, and the level of parathyroid hormone is elevated too, the differential should proceed for that of calcipenic rickets (see below).

Alternatively, if the serum phosphorus is not reduced and the activity of alkaline phosphatase is not elevated, then the level of serum magnesium should next be measured. If the serum magnesium level is markedly reduced (usually to levels below 1 mg per dL), the function of the extracellular calcium-sensing receptor can be so inhibited as to reduce both synthesis and secretion of parathyroid hormone, producing hypocalcemia. If the serum magnesium is not markedly reduced, the measurement of the blood level of parathyroid hormone should be performed.

An inappropriately normal or reduced parathyroid hormone level in the face of hypocalcemia suggests hypoparathyroidism, which may be familial (autosomal-recessive, -dominant, or X-linked), associated with the DiGeorge anomaly (most commonly part of a contiguous 22q11 syndrome including congenital heart disease and thymic hypoplasia), be a part of other syndromes such as Kearns-Sayre syndrome, other mitochondrial cytopathies, autoimmune endocrinopathy type I, and Kenney-Caffey syndrome, among others) secondary to either surgical removal of the glands, or from infiltrative diseases such as hemosiderosis, Wilson disease, or thalassemia. Alternatively, if the serum parathyroid hormone is elevated, the measurement of the serum creatinine provides a differential diagnostic nodal point. With normal kidney function, one of several types of pseudohypoparathyroidism (PHP) is entertained, dependent on the urinary cyclic AMP level (low: PHP-1a or -1c; PHP-1b or elevated: PHP-2). When the kidney function is not normal, concern over CKD–metabolic bone disorder is raised.

Hypocalcemia may be seen in any form of altered vitamin D metabolism, ranging from simple nutritional deficiency in which the measured 25-hydroxyvitamin D blood levels are low through end-organ resistance to the active vitamin D metabolite, 1,25-dihydroxyvitamin D, because of a mutation in the para-nuclear vitamin D receptor.

Hypercalcemia[21,22]

Definition

Hypercalcemia is defined as an increase in serum total calcium >10.2 mg per dL after the first 3 months of life, and within the first 3 months of life, >11 mg per dL.

History and Physical Examination

Symptoms of hypercalcemia include anorexia; weight loss; emesis; altered sensorium; hypertension; extraskeletal calcium deposits in the kidneys (nephrocalcinosis), heart, lungs, and skin among others; bone pain; subcutaneous nodules; and vasopressin resistant polyuria. Radiographs may reveal subperiosteal resorption if the hypercalcemia is mediated by parathyroid hormone excess, and imaging studies may reveal nephrocalcinosis or other extraskeletal deposits of calcium.

Laboratory

In children with hypercalcemia, the level of serum parathyroid hormone provides a differential diagnosis nodal point. If the parathyroid hormone level is elevated or in the normal range in the face of hypercalcemia, and the urinary calcium is increased (normal 24-hour urine calcium excretion is below 4 mg/kg/day), primary hyperparathyroidism should be considered (isolated adenoma, or syndromic in multiple endocrine neoplasia types 1 or 2). Alternatively, if the urinary calcium excretion is reduced in children older than 2 years, or at the lower limits of normal excretion in those younger than 2 years, the entity of familial hypocalciuric hypercalcemia (FHH; due to an inactivating mutation in the extracellular calcium-sensing receptor) should be entertained, and genetic testing considered.

In the child with hypercalcemia and a low level of parathyroid hormone, the level of circulating vitamin D metabolites (25-hydroxyvitamin D; 1,25-dihydroxyvitamin D_3) should be measured, and if markedly elevated, consider either exogenous vitamin D intoxication, or the recently described cause of infantile hypercalcemia associated with a mutation in the vitamin D-24-hydroxylase enzyme, leading to absent inactivation of the active vitamin D metabolite, 1,25-dihydroxyvitamin D and resultant elevated levels.

When the child with hypercalcemia, low level of parathyroid hormone, and normal values for circulating vitamin D metabolites presents to the clinician, the level of PTH-related protein (PTHrp) should be measured, and if elevated, consideration for tumor-associated hypercalcemia or the presence of dysplastic kidneys, which may make the hormone, should be entertained. When PTHrp levels are not elevated, the differential diagnosis revolves around the presence of a recognized syndrome (Jansen osseous dysplasia, Williams syndrome, infantile idiopathic hypercalcemia, hypophosphatasia) or the absence of one (consider phosphate depletion, vitamin A intoxication, adrenal insufficiency, immobilization, sarcoidosis [adolescent age], among others).

Disorders of Phosphorus

Hypophosphatemia[23,24]

Definition

The normal serum phosphorus declines continuously from infancy through adolescence, when it achieves the adult normal values, and a serum phosphorus <2.5 mg per dL defines hypophosphatemia. For reference for other age groups, the normal serum phosphorus is: infants, mean 6.5 mg per dL (range: 4.8–7.4 mg per dL); toddlers, mean 5.0 mg/dL (range: 4.5–5.8 mg per dL); and children, mean 4.4 mg/dL (range: 3.5–5.5 mg per dL).

History and Physical Examination

There may be no symptoms or signs of hypophosphatemia, or the condition may be very symptomatic as intracellular ATP levels decline with impaired oxygen delivery to tissues, producing anorexia, emesis, paresthesias, hyporeflexia, proximal myopathy, rickets, osteomalacia, cardiac failure, respiratory failure, hypotension, rhabdomyolysis, and coma.

Laboratory

Because 99% of the body's phosphorus stores are intracellular, small shifts in extracellular phosphorus can produce profound hypophosphatemia. Such shifts commonly explain hypophosphatemia in hospitalized infants and children, and include infusions of glucose or amino acids in total parenteral nutrition prescriptions, re-feeding in starvation, respiratory alkalosis, and administration of drugs such as insulin, glucagon, androgens, or beta-sympathomimetic agents.

In the absence of a likely redistributional cause of hypophosphatemia, the kidney's ability to reclaim filtered phosphorus becomes an important nodal point in the differential diagnosis. When the kidney reabsorptive capacity is high in the face of hypophosphatemia (calculated tubular reabsorption >90%), primary phosphorus deprivation should be entertained, such as in intestinal malabsorptive diseases, with the use of dietary phosphate binders, alcoholism, or in recovery from vitamin D deficient states (hungry bone syndrome). Alternatively, when the kidney does not reclaim filtered phosphorus in the presence of hypophosphatemia (calculated tubular reabsorption <90%), it is useful to consider measurement of the level of parathyroid hormone (at the time of this writing, the measurement of serum fibroblast growth factor-23 [FGF23] remains a research tool), which when high, indicates hyperparathyroidism. When the level of parathyroid hormone is normal or even suppressed, there may be nonselective kidney wasting of phosphorus, as in Fanconi syndrome, chronic metabolic acidosis, relief from urinary obstruction, or from the effects of glucocorticoids. Selective kidney wasting of phosphorus may occur in one of several forms of hypophosphatemic rickets (see below), oncogenic osteomalacia from PTHrp excess, Jansen osseous dysplasia, or post-kidney transplant tubular dysfunction.

Hyperphosphatemia[25]

Definition

The normal serum phosphorus declines continuously from infancy through adolescence, when it achieves the adult normal values, and a serum phosphorus >4.5 mg per dL defines hyperphosphatemia. For reference for other age groups, the normal serum phosphorus is: infants, mean 6.5 mg per dL (range: 4.8–7.4 mg per dL); toddlers, mean 5.0 mg per dL (range: 4.5–5.8 mg per dL); and children, mean 4.4 mg per dL (range: 3.5–5.5 mg per dL).

History and Physical Examination

Hyperphosphatemia is often asymptomatic when chronic in nature. Acute rises of serum phosphorus may precipitate hypocalcemia with its many associated symptoms (see Hypocalcemia). Chronic hyperphosphatemia may be associated with progressive extraosseous calcifications, or an acute calciphylaxis syndrome with rapid subcutaneous and small blood vessel calcification leading to painful necrosis of the skin and subcutaneous tissues.

Laboratory

The kidney can excrete phosphorous when in excess, so the kidney's excretory response becomes a nodal point for differential diagnosis. When the urine phosphorus is high (tubular reabsorption of phosphorus <85%), either acute redistribution into the intravascular volume (acute metabolic acidosis) or increased enteral absorption (enemas containing phosphate salts, vitamin D intoxication) should be entertained. More commonly, the child with hyperphosphatemia has a reduced excretion of phosphorus (tubular reabsorption ≥85%), and a search for reduced filtering function (GFR) should be done, as AKI or CKD may be present. If the GFR is normal, and the serum calcium is normal too, acromegaly, tumoral calcinosis, hyperthyroidism, or hyperostosis should be considered. If the calcium is reduced (hypocalcemia), either hypoparathyroidism or pseudohypoparathyroidism can be entertained, depending on finding a reduced or normal/elevated value for parathyroid hormone, respectively.

Disorders of Magnesium[26]

Hypomagnesemia

Definition

Serum magnesium below 1.5 mg per dL defines hypomagnesemia.

History and Physical Examination

Hypomagnesemia is often asymptomatic. Any signs and symptoms may be nonspecific and include nausea, emesis, muscle weakness, and constipation. When serum magnesium levels are below 1.0 mg per dL, signs and symptoms of neuromuscular irritability increase, including tremor, seizures, and altered sensorium. Cardiac signs include tachycardia, premature atrial or ventricular contractions, and prolonged QTc interval that may lead to a fatal torsade de pointes. Hypomagnesemia may lead to hypocalcemia and hypokalemia too (see above for each).

Laboratory

The kidney response to hypomagnesemia provides the initial nodal point in differential diagnosis. When the calculated fractional excretion of magnesium is <2%, either a primary decrease in dietary intake (malnutrition, alcoholism, prolonged parenteral fluid use), gastrointestinal losses (malabsorptive syndromes, diarrheal states, short bowel syndrome, laxative abuse, or a primary and selective lack of magnesium absorption in the intestine), or redistribution of blood magnesium (hungry bone syndrome, diabetic ketoacidosis, or re-feeding after starvation) should be entertained.

Alternatively, if the calculated fractional excretion of magnesium is >2%, indicating a renal-generated hypomagnesemia, specific genetic defects (Gitelman syndrome, one of several known mutations in magnesium-transport proteins, or autosomal-dominant hypoparathyroidism) may be entertained, or acquired disorders, such as from drugs (loop diuretics, thiazide diuretics, calcineurin inhibitors, aminoglycoside antibiotics, amphotericin B, or cisplatinum), during a postobstructive diuresis, recovery from AKI, or following kidney transplantation should be entertained.

Hypermagnesemia

Hypermagnesemia is often asymptomatic, as evidenced by women infused with magnesium during premature labor, in whom levels of 4 to 6 mg per dL are well tolerated. Symptoms attributable to hypermagnesemia include lethargy and confusion, muscle weakness, and cardiac irritability with arrhythmias.

There are no primary genetic abnormalities that result in hypermagnesemia, which is, therefore, almost always from excessive intake and diminished kidney excretion. Excessive intake in children may result from the use of magnesium-based laxatives, antacids, or herbal supplements that contain the mineral. In patients treated with lithium for psychiatric disorders, mild hypermagnesemia may occur due to the lithium ion interference with renal magnesium excretion. AKI, CKD, or ESRD, accompanied by increased magnesium intake and/or volume depletion, may predispose to the development of hypermagnesemia. Generally, cessation of the offending agent and restoration of circulating blood volume is sufficient for relief of hypermagnesemia. Severe cardiac instability with hypermagnesemia may require acute dialysis or chronic renal replacement therapy (CRRT).

RICKETS[27]

Rickets (see also disorders of serum calcium and phosphorus) is a term used to note the inability to mineralize osteoid in the growth plates of growing infants, children, and adolescents. As such, the term does not connote a unique disease entity, but is associated with many diseases that impair some critical aspect of healthy bone mineralization. In the past, it has been synonymous with vitamin D deficiency, and although this produces much rachitic disease, the clinician is urged to separate the two entities so that a more complete differential is available.

Rickets may present with hypercalcemia, normocalcemia, or hypocalcemia, and as such, the clinician may be asked to consult upon a patient with a disorder of serum calcium, in which rickets appears as well. Thus, we discuss rickets based on the concurrent levels of blood calcium. Radiographic similarities to rickets but in which other disease processes have been identified as primary abnormalities have been termed pseudorickets, but in general, are very hard to differentiate based on radiographic findings alone.

Regardless of etiology of the rachitic process, there are some general features that are worth noting (Table 64.9). The inability to mineralize bony tissue normally leads to a softening of bone (the original meaning of the word, rickets), and thus, unusual deformities. Such deformities occur most commonly in the bones that are growing the most at a given age. In the neonate, the skull mineralizes after birth, and neonatal rickets may produce a unique softening called the ping-pong ball skull in which gentle pressure against the skull can produce an indentation similar to that seen in ping-pong balls with such pressure. MacEwen crackpot sound has been ascribed to this indentation with pressure, but we discourage the attempt to produce the phenomenon, as brain injury may be induced. In younger infants who may not be walking, angular deformities of the wrists and a heaping up of the osteoid at the costochondral junction (rachitic rosary) are features that can be assessed by the astute clinician. In the toddler with rickets, a bowing out of the legs at the knees is quite common (valgus deformity), whereas in the older child and adolescent, the opposite changes (varus deformity, knock-knee) may be seen. As a general rule, rachitic bone is not a fracturing disease, but many fracturing diseases of childhood may have concomitant vitamin D deficiency–associated rickets.

When confronted with a patient with rickets, the diagnostic scheme should include the blood levels of calcium (and consideration for ionized calcium), phosphorus, magnesium, parathyroid hormone, 25-hydroxyvitamin D (the nutrient

64.9 Classification of Rickets Based on Serum Calcium Levels[a]

Hypercalcemia	Normocalcemia or Hypocalcemia
Neonatal severe primary hyperparathyroidism (homozygous activating mutation of the extracellular Ca-sensing receptor)	Vitamin D nutritional deficiency (seen commonly in exclusively breastfed infants, or in infants and young children with extended absence of sunlight exposure, or infants born to vitamin D deficient mothers)
Hypophosphatasia	Renal Fanconi syndrome (resulting from a primary proximal tubular transport disorder most commonly in pediatrics, and including cystinosis, Dents disease, among many others)
Jansen metaphyseal chondrodysplasia	Hypophosphatemic rickets (due to either a Phex mutation [X-linked dominant hypophosphatemic rickets], DMP-1 mutation [autosomal-recessive hypophosphatemic rickets], FGF23 mutation with active hormone [autosomal-dominant hypophosphatemic rickets], among others)
Idiopathic infantile hypercalcemia due to PTHrp excess	Malabsorption of vitamin D (including cystic fibrosis, celiac sprue, primary disorder of bile salt metabolism, among others)
Idiopathic infantile hypercalcemia due to genetic absence of the vitamin D-24 hydroxylase	Genetic absence of the liver vitamin D-25-hydroxylase
	Genetic absence of the kidney 25-hydroxyvitamin D-1-α-hydroxylase (once termed vitamin D–dependent rickets, type I)
	Genetic mutations in the vitamin D receptor protein, leading to lack of signaling (once termed vitamin D–dependent rickets, type II)
	Chronic kidney disease mineral bone disorder

[a]The list is not an exhaustive one, but lists more commonly seen causes, even if considered "rare."

form of the parent compound vitamin D), and, in selected circumstances, the blood level of 1,25-dihydroxyvitamin D, the kidney-produced active hormone of the vitamin D endocrine system. Prompt attention to severe hypocalcemia is warranted to prevent life-threatening muscle failure, including respiratory failure or heart failure. Conduction system abnormalities should be evaluated with a formal electrocardiogram as well, and the patient monitored if indicated based on those findings.

Treatment of specialized forms of rickets is beyond the scope of our task, but simple nutritional rickets from insufficient dietary vitamin D intake and lack of production of vitamin D by the skin, responds easily to vitamin D replacement alone.

POLYURIA[28–32]

Definition

Polyuria is arbitrarily defined as urine output exceeding 2 L per m^2 in children. Polyuria can be discussed according to the measured urine osmolarity, and can be divided into:

1. Conditions in which there is a primary defect in the ability to maximally concentrate the urine, as reflected by a urine osmolarity of less than 250 to 300 mOsm per kg H_2O (hyposthenuric urine; "dilute polyuria") leading to solute-free water loss and hypernatremia.
2. Kidney diseases associated with tubular salt wasting and relatively fixed urine concentration of about 300 mOsm per kg H_2O (isosthenuric urine). Increased urine output that approaches the degree consistent with polyuria can be observed with the alleviation of urinary tract obstruction and is termed postobstructive diuresis.
3. Excessive renal solute load with a secondary increase in urinary water excretion, producing a urine of greater than 300 mOsm per kg H_2O (concentrated urine initially, but if prolonged, can be associated with isosthenuria, as the hypertonic medullary interstitial gradient is reduced or eliminated). This condition is also referred to as an osmotic diuresis and can be seen in the context of uncontrolled diabetes mellitus, or result from high protein feedings (increased urea load) in neonates or very young infants.

Dilute Polyuria: Differential Diagnosis

Excessive water consumption as in primary polydipsia may occur in children as in adults, but may result also from inappropriate water intake when powder-based infant formulas are mixed improperly, or inappropriate water is fed to infants on purpose by caretakers (termed Munchausen syndrome-by-proxy).

Inappropriately dilute urine can reflect complete or partial antidiuretic hormone (ADH) deficiency, a condition known as central diabetes insipidus (CDI). This condition is most often idiopathic (possibly due to autoimmune injury to the ADH-producing cells in the posterior hypophysis), familial with autosomal-dominant inheritance, or can be induced by pituitary tumor or surgery, head trauma, or hypoxic or ischemic encephalopathy.

Impaired responsiveness of the collecting duct to ADH action is referred to as nephrogenic diabetes insipidus (NDI). NDI is characterized by normal ADH secretion, but varying degrees of renal resistance to the water-retaining effect of the hormone. There are numerous conditions that have been associated with ADH resistance and may lead to symptomatic polyuria as a result of acquired NDI, although generally presenting later in childhood and adolescence compared to hereditary forms.

A variety of renal diseases have been associated with loss of ability to concentrate urine, including release of bilateral urinary tract obstruction,[41] sickle cell disease or trait, inherited renal cystic diseases collectively termed nephronophthises or ciliopathies, renal amyloidosis, hypodysplasia, and Sjögren syndrome.

Common Causes of Acquired NDI

The most common causes of ADH resistance severe enough to produce polyuria are hereditary NDI in children, and chronic lithium ingestion and hypercalcemia in adults. Acquired causes, particularly lithium and other drugs, are at least partially reversible with cessation of therapy or hypercalcemia.

There are also several congenital polyuric-polydipsic Bartter-like syndromes associated with urinary concentrating defects of varying severity.

Lithium

Polyuria due to impaired urinary concentrating ability occurs in up to 20% of patients chronically treated with lithium; an additional 30% have a subclinical impairment in concentrating ability. These adverse effects are mediated by lithium entry into the principal cells in the collecting tubule via the epithelial sodium channel (ENaC).

Hypercalcemia

A renal concentrating defect may become clinically apparent if the plasma calcium concentration is persistently above 11 mg per dL (2.75 mmol per L). This defect, which is generally reversible with correction of the hypercalcemia, may be associated with reductions both in sodium chloride reabsorption in the thick ascending limb of the loop of Henle, thereby interfering with the countercurrent mechanism, and in the ability of ADH to increase collecting tubule water permeability.

Hypokalemia

Persistent, severe hypokalemia (< 3 mEq per L) can impair urinary concentrating ability. As with hypercalcemia, both decreased collecting tubule responsiveness to ADH (which may be mediated by decreased expression of aquaporin-2) and diminished sodium chloride reabsorption in the thick ascending limb have been demonstrated in experimental animals.

History

Age of onset of polyuria may suggest the nature of the underlying disorder. Most hereditary forms of NDI present with severe polyuria during the first weeks to months of life. In familial central DI, usually an autosomal-dominant disease, polyuria may present only after the first year of life, and sometimes in young adulthood, due to preservation of function of the normal allele. The new onset of nocturia or secondary enuresis may be the first clue to DI. The urine is normally most concentrated in the morning due to lack of fluid ingestion overnight; as a result, the first manifestation of a loss of concentrating ability is often nocturia. Family history can be important to demonstrate familial forms of both central and nephrogenic DI. Measurement of urine output by obtaining a timed urine collection of 24 hours—or even a mid-day, 8-hour collection—may be helpful in confirming the presence of polyuria in children.

Laboratory

Comparing plasma sodium concentration and osmolarity to urine osmolarity is key in distinguishing between the three common causes of hyposthenuric polyuria: primary polydipsia, central DI, or nephrogenic DI. A low plasma sodium concentration (less than 135 mEq per L) with a low urine osmolality (e.g., less than one-half the plasma osmolality) is usually indicative of water overload due to primary polydipsia. A high-normal plasma sodium concentration (greater than 142 mEq per L, due to water loss) points toward DI, particularly if the urine osmolality is less than the plasma osmolality. A normal plasma sodium concentration is not helpful in diagnosis but, if associated with a urine osmolality more than 600 mOsmol per kg H_2O excludes a diagnosis of any form of DI.

Diagnosis

Water Deprivation Test

Water restriction can be helpful in confirming the concentration defect and in distinguishing NDI from CDI. It should only be undertaken under careful medical supervision by a physician familiar with its performance and interpretation. The water deprivation test is not necessary to perform if

the plasma sodium concentration is greater than 145 mEq per L and the urine osmolality is less than the plasma osmolality.[7] Water restriction is also important to differentiate CDI from primary polydipsia. Once the plasma osmolality reaches 295 to 300 mOsmol per kg H_2O (normal 275 to 290 mOsmol per kg H_2O) or the plasma sodium is 145 mEq per L or higher, the effect of endogenous ADH on the kidney is maximal. At this point, administering desmopressin will not further elevate the urine osmolality unless endogenous ADH release is impaired as in CDI. Administration of 1-desamino-8-D-arginine vasopressin (DDAVP), a synthetic analogue of the natural arginine vasopressin, is expected to produce a high and prolonged antidiuretic effect in patients with impaired secretion of ADH. Withholding water (e.g., for diagnostic or surgical procedures) can result in severe dehydration. For safety reasons water deprivation should be discontinued in children once 3% of total body weight has been achieved irrespective of plasma osmolarity and sodium levels. After DDAVP administration, patients with NDI are unable to increase urinary osmolality, which remains below 200 mOsm per kg H_2O (normal $\geq$807 mOsm per kg H_2O) and such patients cannot reduce urine volume or free-water clearance. Plasma vasopressin levels are normal or only slightly increased in affected children.

Exceptions to this general rule for performance of a water deprivation test are patients with a dilute urine (i.e., urine osmolality well below that of the plasma) who are strongly suspected of having NDI (e.g., long-term lithium use), and newborns and young infants who are thought to have hereditary NDI. In these patients who are resistant to ADH, the response to desmopressin can be evaluated without prior water restriction.

RENAL DISEASE

Oliguria and Anuria[33–35]

Oliguria occurs when the urine output is below 400 mL/m^2/day, whereas anuria is the complete cessation of urine output. Either may be the initial manifestation of kidney disease in infants and children.

The anuric child must be evaluated for complete urinary obstruction (postrenal kidney failure) and appropriately managed by determining the etiology. The absence of a radiographic demonstration of urinary obstruction leads to the diagnosis of AKI, and management that is not different than the adult with AKI. The majority of neonates urinate in the first 48 hours of life, although a substantial number of infants who urinate at delivery are missed as having made urine. Therefore, consideration of anuria in the newborn should take this into account, especially when kidney function is normal.

Oliguric children should be evaluated based on the history and physical examination evidence of their intravascular volume status. The majority of children who are oliguric have a recognized cause of volume depletion that is extrarenal, and rehydration will produce urine above the oliguric level in the first 12 to 24 hours. The absence of such urine output, and perhaps the absence of response to a potent loop-active diuretic, defines AKI in this situation too. Euvolemic children with oliguria who have a fluid challenge with or without loop-active diuretics and do not resolve the oliguria have AKI as well. Most children with oliguria do not have a hypervolemic state that is not easily explained by aggressive fluid administration often in the hospital setting. Diuretic management of the hypervolemic, oliguric child should be initiated, and if unsuccessful, extracorporeal therapy for AKI should be considered strongly.

In some infants or young children, acute urinary retention may produce oliguria or anuria, but with normal kidney filtering function. The key finding on an ultrasound examination of the abdomen is a full but normal urinary bladder, and in such cases, placing the patient in a warm bath with supervision often leads to a spontaneous diuresis.

The differential diagnosis of AKI in the neonate involves extrarenal diseases such as volume depletion from perinatal issues of blood loss (hemorrhage, twin-twin transfusion), inadequate fluid intake due to environmental stressors such as phototherapy, high environmental temperatures, or any known cause of extrarenal volume depletion. Ischemia from perinatal asphyxia, aortic cross-clamping during cardiac surgery to repair a congenital heart defect, or severe respiratory distress syndrome of infancy may also produce the symptom. Severe congestive heart failure or cyanotic heart diseases without congestive failure may also produce AKI.

Intrinsic causes of AKI in neonates include bilateral renal agenesis, autosomal-recessive polycystic kidney disease, cortical necrosis, nephrotoxicity from drugs, renal vein thrombosis, renal artery thrombosis (often associated with prior or current use of indwelling umbilical artery catheters and the presence of systemic hypertension), acute pyelonephritis, obstructive uropathies, abdominal masses compressing the renal vessels, or, rarely, complete imperforate penile prepuce.

AKI in the older child and adolescent assume the differential diagnostic categories of the adult too and include, in addition to the previously mentioned causes, vasculitis, thrombotic microangiopathy of STEC-hemolytic uremic syndrome (HUS), atypical HUS, all forms of AGN and rapidly progressive glomerulonephritis, tubule-interstitial nephritis from any cause, kidney stones, obstructive fungal balls, retroperitoneal masses, hematoma, or fibrosing conditions, among others.

HYPERTENSION[36–37]

Diagnostic Approach to Hypertension in Childhood

The notion that hypertension in children is related most commonly to an identifiable abnormality in a specific organ system (i.e., secondary hypertension) has been challenged recently by finding an increasing prevalence of essential hypertension

in the childhood years. Nevertheless, the finding of elevated blood pressure (BP) in children warrants careful evaluation for a specific diagnosis before essential hypertension is assigned.

Definitions

BP increases from infancy through adolescence, and generally is thought to track along given percentiles based on genetic and environmental influences. It is based on observational data and adjusted for the patient's age, gender, and statural height. Measurement of BP should take into account appropriate cuff sizes, as a smaller than appropriate cuff size may elevate normal BP falsely.

Normal BP is defined as values below the 90th percentile for age, gender, and height, in the absence of CKD. Prehypertension is average BP values that are ≥90th but <95th percentile. Stage 1 hypertension is systolic and/or diastolic BP ≥95th percentile and stage 2 hypertension is BP >99th percentile.

Hypertensive urgency is severe hypertension with possible end-organ damage in the heart, eye, or kidney, and with a high potential of progressing to a malignant hypertension phase. Hypertensive emergency/malignant hypertension is severe hypertension with symptoms such as headache, vomiting, encephalopathy, or evidence of pulmonary edema, AKI, stroke, or myocardial ischemia.

Technique of Measurement

Obtaining an accurate BP reading using an appropriate size cuff, comprising two thirds of the arm length, is critical in children. Ausculatory BP measurement taken on the upper extremity is considered the preferred method in pediatrics, but on finding an elevated BP, four extremity BP recordings are recommended to evaluate for a coarctation of the aorta, a secondary cause of hypertension in children of any age.

Diagnosis

The findings of at least three abnormal BP readings are often sufficient to establish the diagnosis of hypertension, especially if accompanied by evidence of end-organ damage. Ambulatory BP monitoring (ABPM) is a valuable tool in the diagnosis of "white coat" hypertension or masked hypertension and data regarding the normal values in children are available.

Differential Diagnosis

Secondary hypertension in childhood may be attributed to kidney pathology and accompanied renal parenchymal damage (e.g., polycystic kidney disease, GN, or Wilms tumor), or impaired renal perfusion, also known as renovascular hypertension, as in fibromuscular dysplasia, neurofibromatosis, and systemic vasculitides (e.g., Takayasu arteritis, Moyamoya, Kawasaki). Endocrinopathies such as pheochromocytoma, Cushing syndrome, hyperthyroidism, hyperaldosteronism, and hypercalcemia from various mechanisms are known causes of hypertension in children. Of the cardiovascular causes of secondary hypertension coarctation of the aorta (thoracic and abdominal) is the most recognizable condition. Not uncommon as a group are monogenic disorders (autosomal-dominant [AD] or -recessive [AR]) that may result in hereditary or sporadic hypertension and include Liddle syndrome (AD), apparent mineralocorticoid excess (AR), glucocorticoid remediable aldosteronism (AD), pseudohypoaldosteronism type 2 (AD), and congenital adrenal hyperplasia (11–β hydroxylase deficiency and 17–α hydroxylase deficiency).

Other secondary causes of elevated blood pressure in pediatrics include obstructive sleep apnea, or drug-induced hypertension (e.g., sympathomimetics, cocaine).

Essential hypertension has been increasingly recognized in children and has been linked to the high prevalence of the metabolic syndrome (i.e., hypertension, insulin resistance, hyperlipidemia and obesity), but surely occurs in its absence, too. Traditionally, essential hypertension can be diagnosed only after a thorough evaluation for secondary hypertension.

History should include family history and comprehensive review of systems directed at secondary and symptomatic hypertension. Four extremity BP measurments, as noted previously, and performance of a careful physical exam with particular attention to the presence of bruits over carotid, aorta, and renal arteries; funduscopic examination; and palpation of femoral pulses is an integral part of evaluating a child with elevated BP. Skin examination can lead to a diagnosis, as with the findings of café au lait spots (neurofibromatosis), adenoma sebaceum (tuberous sclerosis), and acanthosis nigricans (insulin resistance).

Laboratory evaluation of a child with newly diagnosed hypertension should follow the clinical suspicion raised by the history and physical exam, but baseline laboratory studies should include a serum creatinine, blood urea nitrogen (BUN), electrolytes, CBC with differential, platelet count, and reticulocyte count, thyroid-stimulating hormone (TSH), thyroxine (FT4), renin, aldosterone, urinalysis, and determination of the first morning random urine protein, creatinine, and level microalbumin excretion.

Imaging

Kidney ultrasound may be valuable for demonstration of an underlying condition such as enlarged kidneys in polycystic kidney disease, small kidneys in advanced CKD from any cause, and size discrepancy in long-standing unilateral renovascular lesions. Doppler studies of the renal vessels have low sensitivity and specificity in diagnosing renal vascular stenosis, and MRA and/or formal contrast-injected radiologic angiography (gold standard) are indicated based on clinical suspicion. An echocardiogram is important in the diagnosis of cardiovascular anomalies (e.g., thoracic coarctation), and in evaluating left ventricular (LV) hypertrophy or LV mass index. The finding of posterior reversible encephalopathy syndrome (PRES) on brain MRI is diagnostic of hypertensive-induced central nervous system injury.

Further diagnostic evaluations should be tailored to the individual patient based on the clinical suspicion and might

include plasma metanephrines/catecholamines (pheochromocytoma), for example.

ABDOMINAL MASSES

A common approach to abdominal masses includes a careful history and physical examination, and multimodal kidney imaging including ultrasound, abdominal CT, MRI, and others as indicated. Care should be taken with the use of MR-contrast agents in children with diminished filtration, as the risk of systemic sclerosing nephropathy may occur during the childhood years too. A skilled pediatric urologist and pediatric surgeon are required almost always for surgical intervention in neonates and children with kidney masses. When malignancy is proven, consultation with a major pediatric center for cancer is required as well.

In the newborn, abdominal masses may include the kidney, where unilateral or bilateral kidney masses may occur. Cystic diseases of the newborn kidney that may produce such masses include autosomal-recessive polycystic kidney disease with large hyperechoic kidneys (and a history of oligohydramnios), autosomal-dominant polycystic kidney disease (large hyperechoic kidneys with or without demonstrable cysts, and often, unilateral in infancy), unilateral multicystic dysplastic kidney (in which the ureter is atretic or absent, the parenchyma is without any function, and other kidney abnormalities are common [vesicoureteral reflux, contralateral uteropelvic junction obstruction]), and rarely, glomerulocystic kidney disease (cortical cysts and CKD). Outside the newborn period, additional cystic kidney diseases include tuberous sclerosis with angiomyolipoma formation, neurofibromatosis, or cystic nephromas.

Tumors of the kidney that produce kidney masses may occur at all ages within pediatrics, and include Wilms tumor, mesoblastic nephromas, clear cell cancer, malignant rhabdoid tumor, nephroblastomatosis (residual metanephrogenic tissue in the mature kidney), hematologic malignancies of leukemia or lymphoma that invade one or both kidneys, neuroblastoma that involves the kidney by extension, and rare tumors of kidney adenomatoid malformation, histiocytic medullary reticulocytosis, or Castleman disease (a form of a lymphoproliferative disorder).

Obstructive lesions of the kidney may produce nephromegaly, including obstruction at the level of the ureteropelvic junction, the uterovesical junction, the presence of posterior urethral valves, or in prune belly syndrome, in which the abdominal musculature is extremely lax, and the peristaltic functions of the ureter is diminished to absent.

Congenital kidney malformations that produce nephromegaly include those in Beckwith-Wiedemann syndrome, horseshoe kidney, duplex kidney, pelvic kidney location, and crossed-fused renal ectopia. Kidney masses associated with infection may produce nephromegaly too, including abscess or urinoma. Hematomas from any etiology may produce a mass and enlargement. Rarely, children may have xanthogranulomatous pyelonephritis and kidney enlargement.

NEPHROLITHIASIS[38–42]

Kidney stones occur about one tenth less frequently in children than in adults, representing from 1 in 1000 to 1 in 7600 pediatric hospital admissions. They are most common in white children, and overall, tend to affect boys and girls equally. This differs from the adult disease, in which there is a male preponderance (3:l). Within subtypes of stone disease, however, male children do have a slightly higher incidence of stones related to hypercalciuria and urinary tract abnormalities. Predisposing factors for nephrolithiasis can be determined in the majority of children affected. These include metabolic abnormalities, UTI in 14% to 75%, and coexisting structural urinary tract abnormalities in about 40%. The recurrence rate of kidney stones in children has been reported as anywhere from 6.5% to 54%, and children with metabolic disorders are nearly five times more likely to have a recurrence. Calcium oxalate stones are the most common found in children, with a frequency of 45%. These are followed by calcium phosphate (14%–30%), struvite (13%), cystine (5%), uric acid (4%), and mixed stones (4%).

Clinical Evaluation

The clinical presentation of urinary tract stones in children may differ from that in adults. Urinary tract stones may present with abdominal, flank, or pelvic pain in only 50% of children with nephrolithiasis. Gross or microscopic hematuria (occurring in 33% to 90% of affected children), dysuria, frequency, emesis, and UTIs are additional common presenting signs in younger patients. A detailed history and physical should guide evaluation of kidney stones. Family history should focus on members with kidney stones (positive in greater than one third of affected children), gout, arthritis, or CKD. The presence of a concomitant UTI must be sought but should not be accepted as the cause of the stone. Patients should also be advised to submit any passed stones or stone fragments for analysis by polarization microscopy or X-ray diffraction but not by simple chemical analysis.

Useful imaging studies may include plain abdominal radiology, ultrasonography, and helical CT. Conventional abdominal radiographs may show only radiopaque but not radiolucent stones, whereas ultrasound of the urinary tract may show both radiolucent and radiopaque stones, in addition to the presence of urinary obstruction or nephrocalcinosis. Ultrasound has largely taken the place of intravenous pyelography (IVP) as an initial study for stone presence, secondary to concerns about radiation and contrast exposure with the latter procedure. Noncontrast helical CT has been found to have high sensitivity and specificity in identifying even small stones without requiring intravenous contrast administration. It may precisely localize stones, detect obstruction and hydronephrosis, and is much more sensitive than the previously mentioned imaging modalities.

Because the majority of children with stones may have a metabolic problem that is discoverable and generally amenable to therapy, diagnostic urinary and blood tests for stone

evaluation should be obtained while the patient is on their routine activity schedule and diet. At least two 24-hour urine collections should be performed, waiting at least 2 weeks after any acute stone event. This time frame allows for the resumption of the child's normal intake of food and fluids after recovery from pain and/or surgical intervention, which is critical for correct assignment of metabolic disturbances. These collections can assess urinary volume as a reflection of fluid intake and creatinine excretion for completeness of the 24-hour collection (at least 10–15 mg/kg/d in children >2 years of age; 6–9 mg/kg/d <2 years of age) and measurement of levels of lithogenic substances such as calcium, oxalate, uric acid, and cystine. The collections can evaluate for the decreased stone inhibitor levels as well, such as citrate and magnesium. Normal values of these substances are shown in Table 64.10. Serum levels of uric acid, potassium, calcium, phosphorus, creatinine, bicarbonate (total CO), and biointact PTH (if hypercalcemia is present) should be obtained as well at the end of the urinary collections. Consultation with an expert in pediatric stone disorders is encouraged if questions arise about the results of these diagnostic studies.

Metabolic Abnormalities in Children with Nephrolithiasis

Hypercalciuria

Calcium oxalate and calcium phosphate stones in children are most frequently caused by hypercalciuria, defined as a urinary calcium excretion of >4 mg/kg/d. Patients with hypercalciuria may present with microscopic or gross hematuria, dysuria, or urgency, even in the absence of any stones. Such children often have a positive family history of kidney stones and may have up to a 17% chance of subsequently developing urolithiasis. Familial idiopathic hypercalciuria is the most common subset of hypercalciuria. Although the genetic basis of this condition is unknown, it seems to be inherited in an autosomal-dominant pattern with incomplete penetrance. The pathophysiology of familial idiopathic hypercalciuria (FIH) is not yet well defined but may include any combination of the following, to varying degrees: a primary kidney tubular reduction in calcium resorption, increased dietary calcium absorption in the gastrointestinal tract secondary to excessive 1,2S-dihydroxy-vitamin D action, and increased bone resorption. The contribution of bone resorption to this disorder has important clinical implications, because restricting calcium intake in these patients may worsen their propensi-ty toward significant osteoporosis.

Causes of hypercalciuria are listed in Table 64.11. Dents disease is an X-linked recessive condition of nephrolithiasis

64.10 Normative Data for Urinary Solute Excretion

Substance	Reference Range
Calcium	≤4 mg/kg/day
Citrate	>400 mg/g creatinine spot citrate/creatinine ratio >0.51 g/g
Oxalate	≤0.5 mmol/1.73 m^2 BSA/day <40 mg/1.73 m^2 BSA/day
Uric acid	Varies with age in pediatrics, rising to 815 mg/1.73 m^2 BSA/day by adolescence
Cystine	<60 mg/1.73 m^2 BSA/day

BSA, body surface area.

64.11 Causes of Hypercalciuria

Associated with Hypercalcemia	Associated with Normal Levels of Blood Calcium
Primary hyperparathyroidism	Familial idiopathic hypercalciuria (FIH)
Idiopathic infantile hypercalcemia	Bartter syndrome
Vitamin D-24-hydroxylase deficiency	Dents disease
Immobilization	Familial hypomagnesemia-hypercalciuria
Thyrotoxicosis	Immobilization
Addison disease	Prematurity ± furosemide
Williams syndrome	Ketogenic diet
PTHrp excess	Distal (type 1) RTA
Osteolytic bone metastases	Medullary sponge kidney
Extra-renal production of calcitriol (Sarcoid, cat-scratch disease, hematologic malignancies)	Systemic inflammatory diseases (e.g., inflammatory bowel disease, juvenile arthritis)
Vitamin D intoxication	Corticosteroid therapy
Jansen metaphyseal chondrodysplasia	Activating mutation of the extracellular calcium-sensing receptor, often associated with hypocalcemia

and subsequent kidney failure, linked to mutations in the CLCN5 gene. This gene is responsible for the transduction of a voltage-gated chloride channel in the kidney, the lack of which leads to hypercalciuria, low molecular weight proteinuria, nephrolithiasis, nephrocalcinosis, and varying degrees of glycosuria, aminoaciduria, and phosphaturia. Bartter syndrome occurs with one of a series of mutations of genes coding for transporters in the thick ascending limb of the loop of Henle. These genes include NKCC2, which transduces the Na-K-2CI transporter (type I Bartter syndrome); ROMK, which transduces the potassium channel (type 11); and CLCNKB, which transduces the chloride channel (type 111). There is also a type IV Bartter syndrome, or Bartter syndrome with sensorineural deafness, which is caused by a mutation in the gene for barttin, a P-subunit of the chloride channel. Type V has a similar phenotype as type IV but is caused by defects in one or both of the chloride channels that co-localize with barttin: C1C-Ka and C1C-Kb.

Distal renal tubular acidosis (dRTA) is a condition of metabolic acidosis, growth retardation, hypercalciuria, and nephrocalcinosis. When associated with a mutation in the ATP6Bl gene responsible for a vacuolar H+-ATPase, it is associated with deafness and an autosomal-dominant inheritance. Familial hypomagnesemia-hypercalciuria is associated with a mutation in the PLCN-1 gene for the tight junction protein paracellin-1. Pseudohypoaldosteronism type I1 is seen with mutations in WNK kinases expressed in the distal nephron and presents with hypertension, hyperkalemia, and metabolic acidosis in addition to hypercalciuria. Other causes of hypercalciuria with normocalcemia include medullary sponge kidney, systemic inflammatory diseases, and iatrogenic resulting from medications such as loop diuretics and corticosteroids. If hypercalcemia is detected, primary hyperparathyroidism, sarcoidosis, immobilization, thyroid disease, osteolytic metastases, hypervitaminosis D, and Williams syndrome should be considered on the differential.

Hypocitraturia

Hypocitraturia is a contributory cause of nephrolithiasis, because citrate is necessary for the formation of a soluble calcium salt to prevent calcium stone crystallization. Most commonly it is seen in RTA, but it is also present in a subset of patients with familial idiopathic hypercalciuria. Hypocitraturia can also occur in concert with other forms of hypercalciuria, hyperuricosuria, or hyperoxaluria. Chronic diarrhea, a high protein diet, and hypokalemia can also induce low urinary citrate levels and a predisposition to stone formation, because citrate absorption in the proximal tubule is stimulated by intracellular acidosis and potassium depletion.

Hyperoxaluria

Oxalate is a human metabolic product made in the liver and excreted by the kidney, but can also be ingested and absorbed from dietary sources. Type 1 primary hyperoxaluria (PH1) is an autosomal-recessive reduction in or absence of alanine glyoxylate aminotransferase (AGT) activity, leading to increased conversion of glyoxylate to oxalate. Excessive urinary oxalate excretion may lead to crystallization and deposition in the urinary tract and kidney parenchyma. This in turn can result in kidney failure and systemic oxalosis, a clinical situation in which calcium oxalate precipitates in multiple organs and joints. Disease severity in PH1 varies widely. The course may be mild and fully responsive to medical therapy such as vitamin B_6 (pyridoxine) or may present aggressively in infancy with rapid kidney failure and severe systemic manifestations. Because AGT is predominantly expressed in the liver, diagnosis has in the past relied solely on liver biopsy to assess AGT presence and activity. The gene encoding AGT (AGXT), located on chromosome 2q37.3, to date has at least 83 mutations that have been described that either eliminate, or decrease substantially, enzyme activity. The relative ease in modern laboratory medicine at performance of sequence analysis, and the delineation of the molecular basis of many of the mutations behind PH1, has led to the proposal of molecular diagnostic algorithms that may obviate the need for invasive biopsy procedures. A recently reported comprehensive mutation screening across the entire AGXT coding region in 55 probands with PH1 showed a 96% to 98% sensitivity in this population. When limited to sequencing of exons 1, 4, and 7, the sensitivity was 77%. Given the relatively small size of the gene, complete molecular analysis should not be at a prohibitive expense. An algorithm beginning with limited sequencing of exons 1, 4, and 7, followed by direct sequencing of the entire gene if inconclusive, would make intuitive sense and would eliminate the need for liver biopsy in most patients. Type 2 primary hyperoxaluria (PH2) results from a deficiency of activity in the enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR), which is more widely distributed in the human than AGTl, with a predominance in muscle, liver, and kidney. As a group, patients with PH2 seem to have less morbidity and mortality than those with PH1, with a lower incidence of ESRD and an older age at onset of symptoms. Unfortunately, up to one third of patients with PH in some case series present at end stage, when uremia develops. For this reason, PH should be considered in patients with recurrent calcium oxalate nephrolithiasis, unexplained nephrocalcinosis, or unexplained CKD in which the kidneys are echodense with calcium.

Secondary (enteric) hyperoxaluria can result from increased oxalate absorption in the colon caused by small bowel malabsorption of fatty and bile acids. These substances increase colonic permeability to oxalate by binding luminal calcium, freeing unbound oxalate to be absorbed. Epithelial damage in these states also increases colonic absorption, and low dietary calcium intake can exacerbate the condition. Depletion of Oxalobacter formigenes, an enteric oxalate-degrading bacterium, can also contribute to enteric hyperoxaluria. Other rare secondary causes are pyridoxine deficiency (a cofactor for AGT activity) and excessive intake of oxalate-containing foods (rhubarb gluttony) or oxalate precursors (ascorbic acid, ethylene glycol).

Hyperuricosuria

Uric acid is the end product of purine metabolism. Hyperuricosuria may occur either in the face of uric acid overproduction or with normal serum uric acid concentrations and can predispose to both uric acid stones and calcium oxalate nephrolithiasis, acting as a heterotopic nucleation factor. Lesch-Nyhan syndrome (complete deficiency of hypoxanthine-guanine phosphoribosyltransferase) and type 1 glycogen storage disease (glucose-6–phosphatase deficiency) are both inborn errors of metabolism that may present with hyperuricemia and hyperuricosuria/urolithiasis. Gout caused by a partial hypoxanthine-guanine phosphoribosyltransferase deficiency can also cause uric acid nephrolithiasis in older children. Myeloproliferative disorders and other causes of cell breakdown are other secondary causes of uric acid stones. Ketogenic diets, excessive protein intake, and uricosuric drugs such as high-dose aspirin, probenecid, and ascorbic acid can also cause hyperuricosuria. Normal or low serum uric acid levels may be associated with uricosuria secondary to proximal renal tubular defects. These may be caused by a single defect in the renal urate exchanger URAT1 or disorders of generalized proximal tubule dysfunction. Insulin resistance, as seen in type 2 diabetes mellitus and metabolic syndrome, may also predispose to uric acid stones and an overly acidic urine by decreasing renal ammonia excretion and impairing hydrogen ion buffering. In another perturbation of uric acid metabolism, xanthine stones are formed in an autosomal-recessive disorder of the gene for xanthine dehydrogenase, whereby uric acid cannot be formed from xanthine precursors, and the serum uric acid is commonly undetectable or below 0.2 mg/dL.

Cystinuria

Cystinuria is an autosomal-recessive disease of disordered dibasic amino acid transport in the kidney and may occasionally be diagnosed by the discovery of flat hexagonally shaped cystine crystals in the urine. Children with this condition have elevated urinary cystine, ornithine, arginine, and lysine levels, because all of these amino acids share transporters. Mutations of the SLC3AI gene on chromosome 2 and the SLC7A9 gene on chromosome 19 have been identified, and patients may be either homozygous or compound or obligate heterozygotes. Affected homozygous children usually excrete >l000 pmol per g creatinine of cystine by the age of 1 year, with a mean excretion of 4500 pmol per g creatinine, exceeding its solubility and leading to lifelong recurrent nephrolithiasis.

Other Causes of Kidney Stones

Additional clinical situations in which patients are predisposed to forming kidney stones include patients with cystic fibrosis (who may have an absence of the oxalate-degrading bacterium O. formigenes), hyperoxaluria, hypercalciuria, and/or hypocitraturia. Patients taking protease inhibitors, especially the poorly soluble indinavir, may have urinary excretion of crystallized drug product. Patients on a ketogenic diet for seizure control are predisposed to hypercalciuria and/or hypocitraturia.

Surgical Management

The goals of the management of patients with kidney stones are to remove existing stones and prevent stone recurrence, with preservation of kidney function. Pediatric patients usually pass ureteral stones up to 5 mm in size. In the absence of infection or persistent pain, such stones can be safely observed for up to 6 weeks. Larger stones and kidney-located stones, however, require the consideration of surgical intervention, with a goal of achieving and maintaining a stone-free state. Choice of surgical modality depends on stone composition, size, and location along the urinary tract. Shock wave lithotripsy (SWL) uses the generation and focusing of shock wave energy toward the stone. Pulverized fragments are subsequently passed, and multiple treatment sessions are sometimes required. One large pediatric series (n = 344) showed a 92% stone-free rate for renal pelvis stones <1 cm, a 68% rate for stones 1 to 2 cm, and a 50% rate for stones >2 cm. Calyceal stone clearance rates were lower. Overall, stone-free rates in children treated using this procedure have ranged from 67% to 99% in various studies, the highest success rates appearing to be in the youngest children. This procedure seems to be safe in young children and infants, with no evidence of long-term changes in GFR or in functional renal parenchymal scarring before and after treatment in the affected area. Minor complications such as bruising, renal colic, and hematuria may occur with SWL treatment. Small children may require the use of lung shielding to prevent pulmonary contusion, as well as reduced power settings to avoid injury. Ureteral stenting may also be required for larger stone burdens.

In general, large stone burden (>2 cm) and anatomic abnormalities are risk factors for unsuccessful SWL, and alternative urologic approaches should be considered in these cases. Struvite, calcium oxalate dehydrate, and uric acid stones are especially amenable to fragmentation with SWL, whereas cystine, brushite, and calcium oxalate monohydrate stones are all resistant to SWL treatment.

Percutaneous nephrolithotomy is an alternative procedure that may be used alone or in conjunction with SWL in patients with large stone burden, significant renal obstruction, and/or staghorn calculi. It is also commonly used to remove lower pole calculi >1 cm in size. Percutaneous access to the collecting system of the kidney is achieved, and a wire is advanced to dilate the tract to accommodate a nephroscope. Stones may be removed or pulverized under direct visualization, making this approach ideal for complex upper tract stones. A nephrostomy tube is often placed postoperatively, although a small series in adults did show a decrease in pain and recovery time, with no increase in complications. Smaller nephroscopes have made percutaneous nephrolithotomy available for children, with stone-free rates ranging from 83% to 98%. Ureteroscopy is most

ideally used for the removal and/or fragmentation of distal ureteral stones. Whereas SWL has good efficacy for some smaller ureteral stones, stone-free rates in those with stones >10 mm in size have been found to be markedly higher with ureteroscopy (93%) than with SWL (50%). Smaller rigid and flexible ureteroscopes have made this procedure an option for pediatric patients and have made the need for concomitant ureteral balloon dilation (and possible risks of stricture and vesicoureteral reflux) less frequent. Once the ureteroscope is passed, laser energy is used to fragment any visualized stones, and flexible wire baskets can be used to remove fragments. Postoperative stenting may be used to facilitate passage of residual fragments or to prevent ureteral obstruction in the face of edema caused by trauma to the ureteral wall. Stenting is not usually done in uncomplicated procedures, with easy passage of the scope.

Medical Management

Nonspecific management of urolithiasis includes an increase in fluid intake to increase urinary volume, urinary dilution, and induce stone particle motion through the urinary tract. Other specific measures depend on the underlying predisposing diagnosis. Hypercalciuria may be treated with a low sodium diet, thiazide diuretics, and adequate potassium intake. Thiazide therapy (e.g., hydrochlorothiazide 1 mg/kg/d, maximum of 25 mg/d) in FIH significantly decreases urinary calcium excretion and rate of stone formation. A decrease in urinary calcium excretion with thiazide treatment in children with FIH has also been shown. In a population with hypercalciuria from immobilization, 18 of 42 children were found to be hypercalciuric, with a higher rate of fracture. A 3-week course of hydrochlorothiazide and amiloride reduced the mean urinary calcium to creatinine ratio by 57.7%. Dietary calcium intake should not be limited. Citrate therapy (e.g., potassium citrate 2 mmol per kg once daily) is also appropriate in cases of documented hypocitraturia.

Another important issue for some patients is that of bone mineral density in FIH. One study of 40 girls with FIH and their premenopausal mothers showed that bone mass density lumbar spine Z-scores were significantly lower in these patients compared with controls. Others have shown that thiazide treatment, in addition to decreasing urinary calcium excretion, can also improve bone mass density scores in children. Average Z-score improved from −1.3 to +0.22 over 1 year of treatment with hydrochlorothiazide and potassium citrate in one study of 18 children.

The treatment of struvite stones rests on the eradication of stones, correction of any urinary obstruction, and treatment/prevention of UTIs. Urinary acidification could theoretically be used to prevent crystallization, but evidence for such an approach is thus far lacking. The urease inhibitor acetohydroxamic acid may have some clinical use, but its use is limited by a high incidence of neurologic and gastrointestinal side effects.

Hyperuricosuria may be treated with dietary sodium limitation, oral bicarbonate or citrate supplementation, or addition of allopurinol if increased uric acid production and hyperuricemia are present.

Patients with suspected primary hyperoxaluria should be given a therapeutic course of vitamin B_6 (pyridoxine), and urinary oxalate levels should be used to monitor success or to suggest the need for dose escalation. For patients with reduced kidney function, intensive dialysis followed by liver-kidney transplant can be curative, because a new liver replaces the enzymatic defect in PHl. While awaiting transplant, hemodialysis for five to six times per week, and perhaps with additional nightly peritoneal dialysis, is needed to lessen the systemic oxalate burden and prevent recurrence of disease in the transplant kidney. Prompt referral to a pediatric center with expertise in this disorder is suggested.

Secondary hyperoxaluria that results from enteric hyperoxaluria may be treated with a low sodium/low fat diet, high fluid intake, and a dietary calcium intake at the upper end of the daily recommended intake. Limitation of oxalate-containing foods such as chocolate, rhubarb, nuts, and spinach should be advised, as well as possible supplementation with magnesium, phosphorus, and citrate salts.

Cystinuria is treated with fluids (minimum of 3 L/1.73 m^2/d) and provision of alkali salts, such as citrate. Low sodium intake can also decrease urinary excretion of cystine. Chelating agents such as D-penicillamine, or more recently, alpha-mercapto propionylglycine (Thiola; Mission Pharmacal, San Antonio, TX) may also be prescribed by someone skilled in pediatric stone disease. D-penicillamine may cause a severe serum sickness–like reaction, but side effects are less severe with Thiola. Angiotensin converting enzyme inhibition with captopril therapy has been found beneficial in some patients with cystinuria (captopril-cystine complexes are 200 times more soluble than cystine alone) resistant to alkalinization and fluid therapy alone, and perhaps with less bothersome side effects. Captopril, however, is not as effective as thiol compound therapy.

DISORDERS OF SEXUAL DIFFERENTIATION[43,44]

Infants with a congenital discrepancy between external genitalia, gonadal, and chromosomal sex are classified as having a disorder of sex development (DSD). A 2006 consensus conference suggested that the potentially pejorative terms pseudohermaphroditism and intersex be replaced by the diagnostic category disorders of sex development (Table 64.12).

Kidney disease is associated with patients who have DSD. The diseases are those of kidney tumors such as Wilms tumor (Table 64.13) and forms of steroid-resistant nephrotic syndrome, generally leading to ESRD. The role of prophylactic bilateral nephrectomy to prevent the development of the Wilms tumor remains problematic and controversial, but frequent screening with an ultrasound examination is warranted. Newborns with DSD should be promptly referred to a center specializing in the multidisciplinary treatment of such disorders.

64.12 Proposed Revised Nomenclature for Disorders of Sex Differentiation

Previous	Proposed, Current
Intersex	DSD
Male pseudohermaphrodite, undervirilization of an XY male, and undermasculinzation of an XY male	46 XY DSD
Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female	46 XX DSD
True hermaphrodite	Ovotesticular DSD
XY male or XX sex reversal	46 XX testicular DSD
XY sex reversal	46 XY complete gonadal dysgenesis

DSD, disorders of sex differentiation.

Frasier syndrome is characterized as a DSD in which nephrotic syndrome (mostly FSGS) develops, and gonadoblastomas, but not Wilms tumors, predominate.

URINARY TRACT INFECTION[45–47]

UTI can occur in children of all ages. It has been estimated that UTI is diagnosed in 3% of prepubertal girls and 1% of prepubertal boys, with an even higher incidence in pubertal girls. The relative risk of UTI in girls and boys ages 2 months to 2 years is 2.27; this pattern is even more apparent in older children. Few children or adults who have recurrent UTI progress to serious renal disease, but chronic pyelonephritis may cause ESRD. The epidemiology of chronic pyelonephritis is complicated by the virulence of the infecting organism and the specific susceptibility of the child. Investigation of children with UTI has shown that vesicoureteral reflux (VUR) is present in 25% to 33% and that the degree of VUR correlates well with the prevalence of renal scarring. Numerous urinary pathogens possess fimbrial or nonfimbrial (type 1 fimbriae and P-fimbriae) adhesins for mucosal attachment and colonization. P-fimbriated Escherichia coli are associated with the development of renal scars, and inappropriate antibiotic therapy may favor colonization with such organisms. The understanding of UTI and its epidemiology with regard to congenital, genetic, and environmental aspects suggests that early diagnosis and treatment should lead to a reduction in morbidity and mortality rates.

The role of the pediatrician caring for children with UTI is to prevent recurrent UTI and new renal scar formation and consequently renal impairment by facilitating prompt diagnosis of UTI and identifying children with existing renal scars, underlying renal tract anomalies, or known complications of UTI or VUR. Indeed, without an underlying renal tract abnormality, progressive renal damage is rare in children with UTI. Population screening is not cost effective, but early diagnosis by primary health care workers, urgent treatment of acute pyelonephritis to minimize scar formation, and prevention of infection by long-term low-dose prophylactic antibiotics or the surgical correction of reflux in selected children can all contribute to an improved prognosis. Successful management of UTI in childhood by routine urine culture in all febrile infants and toddlers in Sweden has reduced the prevalence of reflux nephropathy/chronic pyelonephritis causing ESRD in pediatric transplant recipients from 20% in the 1970s to less than 5% in the 1990s in that country.

Reflux nephropathy or scarring in the presence of VUR may arise by two main independent mechanisms. Severe antenatal VUR causes segmental renal dysplasia or hypoplasia in the fetal kidney, whereas postnatal VUR with intrarenal reflux and urinary infection causes segmental renal pyelonephritic scars in both infants and older children. The presence of compound renal papillae, which allow the backflow of infected urine from the calyces into the collecting ducts (intrarenal reflux), is important in the generation of renal scars with VUR in animal models; however, the relevance of this mechanism in reflux nephropathy in children has been debated due to the rarity of such papillae in human kidneys. The increased frequency of UTI in infants, the presence of congenital segmental renal dysplasia, the increased risk of true infective pyelonephritic scars developing in infants, and renal impairment at presentation all demonstrate that the target population in which to detect UTI and renal "scars" is children under 18 months of age.

64.13 DSD Syndromes Associated with Wilms Tumor (site of chromosomal aberration)

Denys-Drash (11p13)	Beckwith-Wiedeman (11p15)
WAGR (11p13)	Perlman syndrome
Hemi-hypertrophy	Sotos syndrome (5q35)
Blooms syndrome (15q26)	Simpson-Golabi-Behemel (Xp26)

WAGR, Wilms tumor, aniridia, genital abnormalities, mental retardation.

The clinical presentation of UTI varies with the age of the child. In young children, classic symptoms of UTI such as dysuria, frequency, urgency, and flank pain are uncommon. Instead, vague symptoms such as fever, abdominal pain, irritability, lethargy, poor feeding, or incontinence are frequent. Fever is a common symptom, and the American Academy of Pediatrics advises that UTI be excluded in any child between 2 months and 2 years of age with unexplained fever.

It is critical to obtain an uncontaminated urine sample for diagnosis. Bladder catheterization provides a sterile sample in the infant or incontinent child. Suprapubic aspiration, although providing definitive results in young infants, is difficult to perform in children older than 1 year of age and is becoming less popular. Bag urine specimens often are contaminated and should not be used for diagnosis of UTI. In older continent children, a clean-catch urine specimen can be obtained, but both clean-catch urine and midstream urine specimens can be difficult to acquire, particularly if parents are given the responsibility of obtaining them. A frequent mistake is to diagnose UTI from a significant growth of organisms after culture of a contaminated or improperly transported urine specimen. The specimen should be cultured within 2 hours or transported in a medium such as boric acid that prevents bacterial multiplication.

Most truly infected urines contain an excess of white blood cells and yield a pure growth of a single organism. Fresh urine without cells or visible organisms on microscopy is unlikely to be infected. Although more than 10^5 organisms per milliliter of urine is the standard criterion for UTI in girls, $>10^4$ organisms/mL in boys is highly indicative of a UTI. In infants a moderate growth of 10,000 to 100,000 organisms per milliliter of urine may represent an infection, and further specimens should be obtained. A detailed history about fever accompanying the illness, the adequacy of the urinary stream in boys, and the presence of functional bladder problems, followed by careful palpation of the abdomen for renal masses and bladder enlargement, thorough examination of the genitalia, and assessment of perineal sensation and neurologic function in the lower limbs, should be carried out.

Appropriate investigations depend on the age of the child and the clinical assessment. Several medical committees have published guidelines on appropriate protocols to investigate UTI in children. However, there is significant controversy in the literature regarding the extent and timing of evaluation in children with UTI and the impact that such evaluation has on the development of reflux nephropathy. What is needed is appropriate investigation of all children with UTI if outcomes of children who present in middle or late childhood with ESRD due to reflux nephropathy are to be avoided. At our institution, we recommend renal and bladder ultrasonography in boys of any age with UTI, all girls younger than 5 years of age, and all with pyelonephritis or recurrent UTI. A functional study such as ^{99m}Tc-DMSA renal isotope scan and or voiding cystourethrography can be performed to detect segmental renal dysplasia or scarring in selected cases, including infants, in which an ultrasound study is abnormal. Voiding contrast cystourethrography, if indicated by an abnormal ultrasound examination, is preferred to radionuclide cystography for the initial study, particularly in boys, due to the former's ability to exclude structural anomalies of the urethra including posterior urethral valves. Failure to make the diagnosis, investigate thoroughly, and follow guidelines remain the major obstacles in identifying those children at risk of renal impairment or hypertension.

Management of Urinary Tract Infection

There is little evidence that older children with normal urinary tracts without renal scars who have recurrent UTI will sustain renal damage, and for such children, attention to hygiene, prevention of constipation, and an adequate fluid intake with regular bladder emptying are important. Mild or moderate reflux without upper tract dilation in young children is likely to disappear in a reasonably short time so that, if the kidneys are not scarred, medical management seems appropriate, whereas severe reflux, especially with scarred kidneys, requires longer term follow-up, and surgery may be advisable if the quality of the surgery can be guaranteed. However, the single most important action required to reduce the morbidity and mortality of chronic pyelonephritis is the diagnosis and treatment of UTI in infants with fever.

Management of UTI involves early administration of appropriate antibiotics to treat the infection and reduce the risk of renal scarring, attention to the voiding habits of children and avoidance of constipation, encouragement of good fluid intake and good personal hygiene of the perineum and genitalia, and diagnosis of any underlying renal tract abnormality. Incontinence predisposes to infection, and the treatment of enuresis by bladder training is important. VUR of a significant grade may be treated medically with prophylactic antibiotics at night or surgical reimplantation of the ureter. Nightly prophylactic antibiotics should also be considered for children in the absence of VUR or other renal structural anomalies when attention to fluid intake, hygiene, and other intervention is not successful in prevention of recurrent infection. The International Reflux Study has shown that medical management of VUR is equivalent to surgery in reducing the number of new renal scars. No advantage between medical vs. surgical management has been shown after 5 years of follow-up. Prophylactic antibiotics reduce the incidence of UTI, but doubt has been cast on whether regular prophylactic antibiotics or even surgery significantly alter the rate of new scar formation—most authors agree that making an early diagnosis of UTI is most important in this regard. In those children who continue to reflux, cessation of prophylactic antibiotics after 8 years of age was associated with only 12% risk of another UTI. Antibiotic prophylaxis or surgery alone does not influence the number of children reaching ESRD.

Because most infections are caused by organisms from the bowel, at least in girls, successful antibiotic prophylaxis

depends on the prevention of antibiotic resistance in the bowel flora. Suitable medicines are trimethoprim, 1 mg per kg, or trimethoprim/sulfamethoxazole; nitrofurantoin, 1 to 2 mg per kg; or nalidixic acid, 15 mg per kg, all given as a single dose at night.

The complications of UTI in children include renal scarring and renal calculi. Proteus infections more commonly cause renal calculi than any other infection because of the organism's ability to produce alkaline urine by degrading urea. In long-term follow-up studies of up to 41 years, hypertension was observed in young adults in approximately 10% of cases, with people in the higher percentile range for blood pressure being more at risk than others. Approximately 10% have significant renal impairment and may reach renal failure as young people. UTI, preeclampsia, fetal death, and low-birth-weight infants are more common in women with renal scarring.

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