
سیستم نوبت دهی آنلاین
یادآوری نوبت
به بیماران
اکسیر

Nephrology

PART XXI

Section 1

Glomerular Disease

Chapter 557

Introduction to Glomerular Diseases

557.1 Anatomy of the Glomerulus

Edward J. Nehus

The kidneys lie in the retroperitoneal space slightly above the level of the umbilicus. They range in length and weight, respectively, from approximately 6 cm and 24 g in a full-term newborn to ≥12 cm and 150 g in an adult. The kidney (Fig. 557.1) has an outer layer, **the cortex,** which contains the glomeruli, proximal and distal convoluted tubules, and collecting ducts, and an inner layer, **the medulla,** which contains the straight portions of the tubules, the loops of Henle, the vasa recta, and the terminal collecting ducts (Fig. 557.2).

The blood supply to each kidney usually consists of a main renal artery that arises from the aorta, although multiple renal arteries can occur. The main artery divides into segmental branches within the medulla, becoming the interlobar arteries that pass through the medulla to the corticomedullary junction. At this point, the interlobar arteries branch to form the arcuate arteries, which run parallel to the surface of the kidney. Interlobular arteries originate from the arcuate arteries and give rise to the afferent arterioles of the glomeruli. Specialized muscle cells in the wall of the afferent arteriole and specialized distal tubular cells adjacent to the glomerulus (macula densa) form the juxtaglomerular apparatus that controls the secretion of renin. The afferent arteriole divides into the glomerular capillary network, which then recombines into the efferent arteriole (see Fig. 557.2). The juxtamedullary efferent arterioles are larger than those in the outer cortex and provide the blood supply, as the vasa recta, to the tubules and medulla.

Each kidney contains approximately one million **nephrons** (each consisting of a glomerulus and associated tubules). There is a large distribution of normal nephron numbers in humans, ranging from 200,000 to 1.8 million nephrons per kidney. This variation can have major pathophysiologic significance as a risk factor for the later development of hypertension and progressive renal dysfunction. In humans, the formation of nephrons is complete at 34-36 weeks of gestation, but functional maturation with tubular growth and elongation continues during the first decade of life. Because new nephrons cannot be formed after birth, any disease that results in progressive loss of nephrons can lead to renal insufficiency. A decreased number of nephrons secondary to low birthweight, prematurity, and/or unknown genetic or environmental factors has been implicated as a significant risk factor for the development of primary hypertension and progressive renal dysfunction in adulthood. A low nephron number presumably results in hyperfiltration and eventual sclerosis of *overworked* nephron units.

The glomerular network of specialized capillaries serves as the filtering mechanism of the kidney. The glomerular capillaries are lined by endothelial cells (Fig. 557.3) and have very thin cytoplasm that contains many holes (fenestrations). The **glomerular basement membrane** (GBM) forms a continuous layer between the endothelial and mesangial cells on one side and the epithelial cells on the other. The membrane has three layers: a central electron-dense lamina densa; the lamina rara interna, which lies between the lamina densa and the endothelial cells; and the lamina rara externa, which lies between the

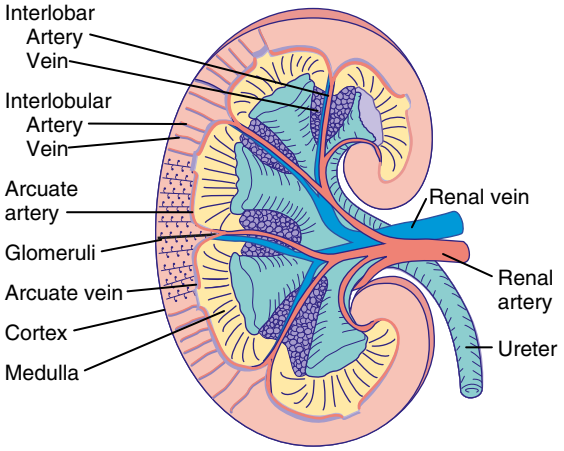

Fig. 557.1 Gross morphology of the renal circulation. *(From Pitts RF. Physiology of the Kidney and Body Fluids, 3rd ed. Chicago: Year Book Medical Publishers; 1974.)*

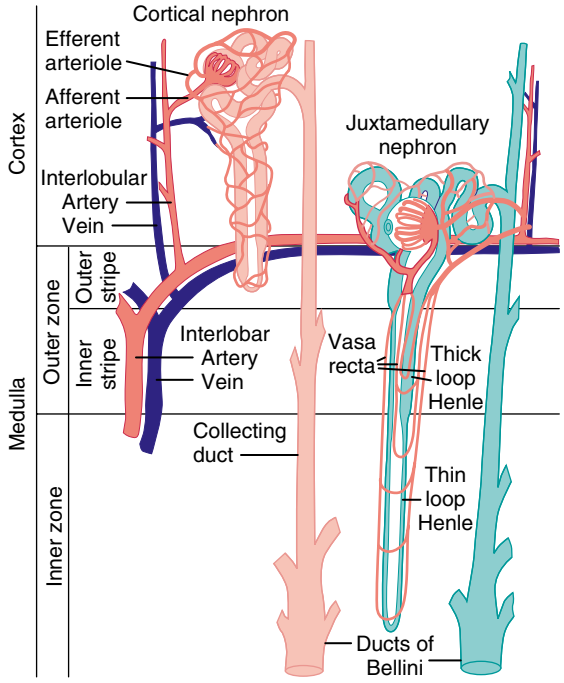

Fig. 557.2 Comparison of the blood supplies of cortical and juxtamedullary nephrons. *(From Pitts RF. Physiology of the Kidney and Body Fluids, 3rd ed. Chicago: Year Book Medical Publishers; 1974.)*

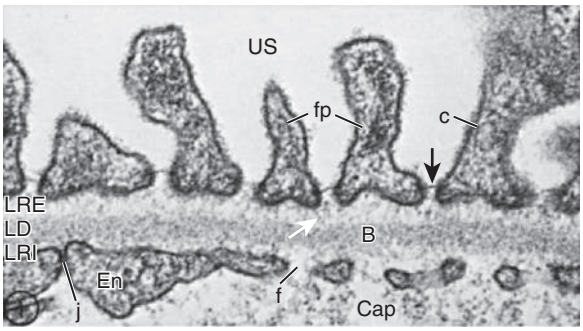

Fig. 557.3 Electron micrograph of the normal glomerular capillary *(Cap)* wall demonstrating the endothelium *(En)* with its fenestrations *(f)*; the glomerular basement membrane *(B)* with its central dense layer, the lamina densa *(LD)*, and adjoining lamina rara interna *(LRI)* and externa *(LRE) (white arrow)*; and the epithelial cell foot processes *(fp)* with their thick cell coat *(c)*. The glomerular filtrate passes through the endothelial fenestrae, crosses the basement membrane, and passes through the filtration slits *(black arrow)* between the epithelial cell foot processes to reach the urinary space *(US)* (×60,000). *j*, Junction between two endothelial cells. *(From Farquhar MG, Kanwar YS. Functional organization of the glomerulus: state of the science in 1979. In: Cummings NB, Michael AF, Wilson CB, eds. Immune Mechanisms in Renal Disease. New York: Plenum; 1982.)*

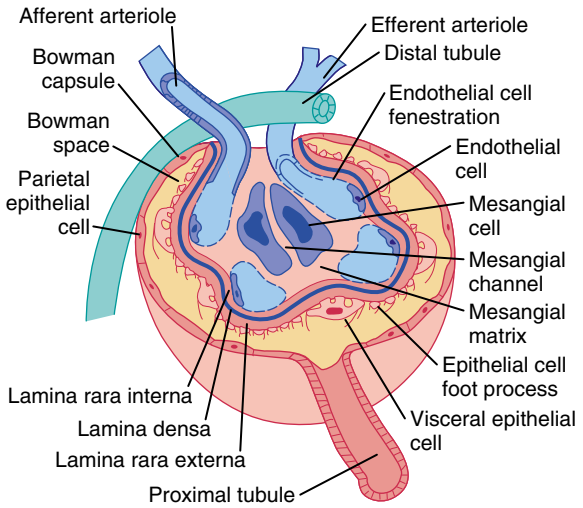

Fig. 557.4 Schematic depiction of the glomerulus and surrounding structures.

lamina densa and the epithelial cells. The visceral epithelial cells cover the capillary and project cytoplasmic foot processes, which attach to the lamina rara externa. Between the foot processes are spaces or filtration slits. The **mesangium** (mesangial cells and matrix) lies between the glomerular capillaries on the endothelial cell side of the GBM and forms the medial part of the capillary wall. The mesangium may serve as a supporting, stalk-like structure for the glomerular capillaries and probably has a role in the regulation of glomerular blood flow, filtration, and the removal of macromolecules (such as immune complexes) from the glomerulus. The Bowman's capsule, which surrounds the glomerulus, is composed of a basement membrane, which is continuous with the basement membranes of the glomerular capillaries and the proximal tubules, and the parietal epithelial cells, which are adjacent to the visceral epithelium (Fig. 557.4).

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557.2 Glomerular Filtration

Edward J. Nehus

Kidney function is best measured as the **glomerular filtration rate (GFR)**. As the blood passes through the glomerular capillaries, the plasma is filtered through the glomerular capillary walls. Small plasma molecules filter freely (e.g., electrolytes, glucose, phosphate, urea, creatinine, peptides, low molecular weight proteins), whereas larger molecules are retained in the circulation (such as albumin and globulins). The filtrate is collected in Bowman's space and enters the tubules. There its composition is modified by tightly regulated secretion and absorption of solute and fluid by the multiple tubular segments of the nephron and the ductal system, until it exits the kidney, via the ureter, as urine.

Glomerular filtration is the net result of opposing forces applied across the capillary wall. The force for ultrafiltration (glomerular capillary hydrostatic pressure) is a result of systemic arterial pressure, modified by the tone of the afferent and efferent arterioles. The major force opposing ultrafiltration is glomerular capillary oncotic pressure, created by the gradient between the high concentration of plasma proteins within the capillary and the almost protein-free ultrafiltrate in Bowman's space. Filtration may be modified by the rate of glomerular plasma flow, the hydrostatic pressure within Bowman's space, and/or the permeability of the glomerular capillary wall.

Although glomerular filtration begins at approximately the sixth week of fetal life, kidney function is not necessary for normal intrauterine homeostasis because the placenta serves as the major fetal excretory organ. After birth, the GFR increases until renal growth ceases (by age ~18-20 years in most people). To compare GFRs of children and adults, the GFR is standardized to the body surface area (1.73 m^2) of an "ideal" 70-kg adult. Even after correction for surface area, the GFR of a child does not approximate adult values until the second to third year of life (Fig. 557.5). The GFR may be estimated by measurement of the serum creatinine level. Creatinine is derived from muscle metabolism. Its production is typically constant, and its excretion is primarily through glomerular filtration, although tubular secretion can become important as the serum creatinine rises in renal insufficiency. In contrast to the concentration of blood urea nitrogen, which is affected by the state of hydration and nitrogen balance, the serum creatinine level is primarily influenced by muscle mass and the level of glomerular function.

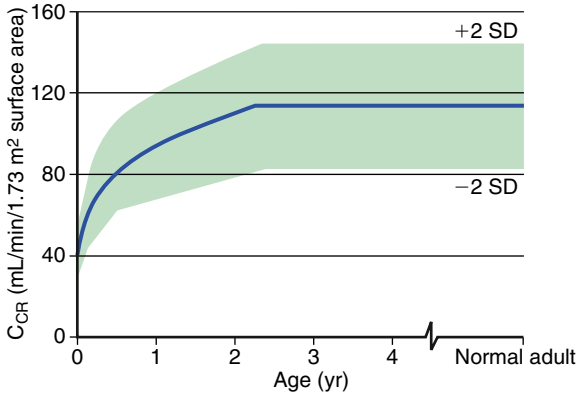

Fig. 557.5 Changes in the normal value of the glomerular filtration rate, as measured by the creatinine clearance *(Ccr)*, when standardized to mL/min/1.73 m^2 of body surface area. The *solid line* depicts the mean, and the *shaded area* includes 2 standard deviations (SDs). *(From McCrory W. Developmental Nephrology. Cambridge, MA: Harvard University Press; 1972.)*

The serum creatinine is of value only in estimating the GFR under steady-state conditions. A patient can have a normal serum creatinine level with decreased renal function very shortly after the onset of acute kidney injury. In this clinical setting, serum creatinine may take days to reach the steady state. Furthermore, kidney function may fall significantly before a noticeable rise in serum creatinine occurs.

The precise measurement of the GFR is accomplished by quantitating the clearance of a substance that is freely filtered across the capillary wall and is neither reabsorbed nor secreted by the tubules. The clearance (C_s) of such a substance is the volume of plasma that, when completely cleared of the contained substance, would yield an equal quantity of that substance excreted in the urine over a specified time. Renal clearance is calculated by the following formula:

$$C_s\left(\text{mL/min}\right) = U_s\left(\text{mg/mL}\right) \times \left(V\left(\text{mL/min}\right) / P_s\left(\text{mg/mL}\right)\right)$$

where C_s equals the clearance of substance s, U_s reflects the urinary concentration of s, V represents the urinary flow rate, and P_s equals the plasma concentration of s. To correct the clearance for individual body surface area, the formula is:

$$\text{Corrected clearance}\left(\text{mL/min/1.73 m}^2\right) = C_s\left(\text{mL/min}\right) \times \frac{1.73}{\text{Surface area}\left(\text{m}^2\right)}$$

The GFR is optimally measured by the clearance of inulin, a fructose polymer having a molecular weight of approximately 5.7 kDa. Because the inulin clearance technique is cumbersome, radioisotopes are commonly used to measure GFR in clinical practice. GFR can be accurately determined by a single intravenous injection of a radioisotope, most commonly ^{99m}TC-DTPA, followed by timed monitoring of serum samples.

Because true measurement of the GFR is expensive and time-consuming, the GFR is commonly estimated (eGFR) by the clearance of endogenous creatinine. Formulas that estimate creatinine clearance accurately in clinical settings have been useful tools in patient care. The "bedside" Schwartz formula is the most widely used pediatric formula and is based on the serum creatinine (S_{cr}), patient height, and an empirical constant:

$$\text{eGFR} = 0.413\,\text{height}\left(\text{cm}\right) / S_{cr}\left(\text{mg/dL}\right)$$

The accuracy of GFR-estimating equations can be further improved utilizing an additional endogenous marker, cystatin C, in addition to serum creatinine. Cystatin C is a 13.6-kDa protease inhibitor produced by nucleated cells that is freely filtered by the kidney. It continues to gain popularity as a clinical tool to provide an alternative to creatinine-based formulas because it has distinct advantages in estimating the GFR. Unlike creatinine, cystatin C is not secreted by the renal tubules under any conditions. Furthermore, it is less affected by sex, age, and muscle mass than serum creatinine. Several cystatin C-based formulas have been developed, including a multivariable eGFR equation that combines both cystatin C and creatinine in addition to height, BUN, and gender:

$$\text{eGFR} = 39.8 \times \left[\text{height}\left(\text{m}\right)/S_{cr}\left(\text{mg/dl}\right)\right]^{0.456} \times \left[1.8/\text{cystatin C}\left(\text{mg/L}\right)\right]^{0.418} \times \left[30/\text{BUN}\left(\text{mg/dl}\right)\right]^{0.079} \times \left[1.076\right]^{\text{male}} \times \left[\text{ht}\left(\text{m}\right)/1.4\right]^{0.179}$$

However, cystatin C assays are not available in many laboratories and lack standardization. Therefore the creatinine-based bedside Schwartz equation remains the most widely used assessment of kidney function in children.

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557.3 Glomerular Diseases

Edward J. Nehus

PATHOGENESIS

Glomerular injury may be the result of a genetic, immunologic, perfusion, or coagulation disorder. Genetic disorders of the glomerulus may result from pathogenic variants in genes encoding proteins located within the glomerulus, interstitium, or tubular epithelium; pathogenic variants in regulatory genes controlling DNA transcription; abnormal posttranscriptional modification of RNA transcripts; or abnormal posttranslational modification of proteins. Immunologic injury to the glomerulus results in **glomerulonephritis,** which is a generic term for several diseases but more precisely is a histopathologic term defining inflammation of the glomerular capillaries. Evidence that glomerulonephritis is caused by immunologic injury includes morphologic and immunopathologic similarities to experimental immune-mediated glomerulonephritis, the demonstration of immune reactants (immunoglobulin, complement) in glomeruli, abnormalities in serum complement, and the finding of autoantibodies (anti-GBM) in some of these diseases (Fig. 557.6). There appear to be two major mechanisms of immunologic injury: glomerular deposition of circulating antigen-antibody immune complexes and direct interaction of antibody with specific glomerular antigens in situ. In the former, antibody is produced against and combines with a circulating antigen that is usually unrelated to the kidney (see Fig. 557.6). The immune complexes accumulate in GBMs and activate the complement system, leading to immune injury. Immunofluorescence microscopy often demonstrates granular or irregular deposits containing immunoglobulin and complement in the glomerular capillary wall. Electron microscopic studies may show these deposits in the GBM and in the mesangium. Examples of circulating immune complex–mediated glomerulonephritis include postinfectious glomerulonephritis, IgA nephropathy, membranoproliferative glomerulonephritis, and lupus nephritis. In situ immune complex formation occurs when an antibody reacts with antigen(s) of the GBM. Immunopathologic studies reveal linear deposition of immunoglobulin and complement along the GBM. This type of immune complex injury occurs in Goodpasture syndrome and membranous nephropathy.

The inflammatory reaction that follows immunologic injury results from activation of one or more mediator pathways. The most important of these is the complement system, which has two initiating sequences: the classic pathway, which is activated by antigen-antibody immune complexes, and the alternative or properdin pathway, which occurs by autoactivation of C3 by a process known as C3 tick over. These pathways converge at C3; from that point on, the same sequence leads to lysis of cell membranes (see Chapter 173). The major noxious products of complement activation are produced after activation of C3 and include anaphylatoxin (which stimulates contractile proteins within vascular walls and increases vascular permeability) and chemotactic factors (C5a) that recruit neutrophils and perhaps macrophages to the site of complement activation, leading to consequent damage to vascular cells and basement membranes.

PATHOLOGY

The glomerulus may be injured by several mechanisms, but it has only a limited number of histopathologic responses; different disease states can produce similar microscopic changes.

Proliferation of glomerular cells occurs in most forms of glomerulonephritis and may be generalized (involving all glomeruli) or focal (involving only some glomeruli and sparing others). Within a single glomerulus, proliferation may be diffuse (involving all parts of the glomerulus) or segmental (involving only one or more tufts, but not others). Proliferation commonly involves the endothelial and mesangial cells and is often associated with an increase in the mesangial matrix (see Fig. 557.6). Mesangial proliferation can result from deposition of

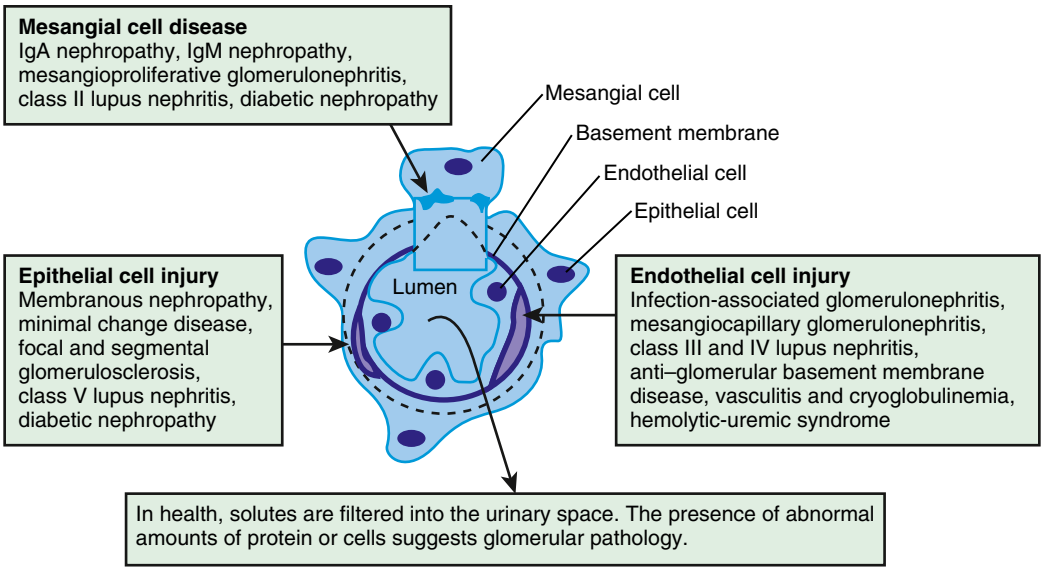

Fig. 557.6 Cellular location of injury during glomerulonephritis. Mesangial cells are directly exposed to the circulation. Deposition of immune complexes within these cells is typically seen in disorders such as immunoglobulin A *(IgA)* nephropathy; it results in proliferation and expansion of the cells, leading to hematuria, proteinuria, and renal impairment. Epithelial cells, in conjunction with basement membrane, allow filtration of plasma solutes but retard passage of cells and plasma proteins. Disease related to these cells is typified by the presence of subepithelial deposits and flattening of the foot processes that engage the basement membrane, resulting in disruption of the filtration barrier and proteinuria. Endothelial cell disease can result from deposition of immune complex (as occurs in mesangiocapillary glomerulonephritis), attachment of antibody to the basement membrane (Goodpasture disease), or trauma and activation of coagulation (hemolytic-uremic syndrome). Endothelial cell proliferation and necrosis are accompanied by leukocyte accumulation; rupture of the basement membrane, crescent formation, and disruption of glomerular architecture can develop. A nephritic or rapidly progressive presentation ensues. *(From Chadban SJ, Atkins RC. Glomerulonephritis. Lancet. 2005;365:1797–1806.)*

immune complex within the mesangium. The resultant increase in cell size and number, and production of mesangial matrix, can increase the glomerular size and narrow the lumens of glomerular capillaries, leading to renal insufficiency.

Crescent formation in Bowman's space (capsule) is a result of proliferation of parietal epithelial cells and is often associated with clinical signs of renal dysfunction. Crescents develop in several forms of glomerulonephritis (termed **rapidly progressive** or **crescentic;** see Chapter 559.7) and are a characteristic response to deposition of fibrin in Bowman's space. Newly formed crescents contain fibrin, the proliferating epithelial cells of Bowman's space, basement membrane–like material produced by these cells, and macrophages that might have a role in the genesis of glomerular injury. Over subsequent days to weeks, the crescent is invaded by connective tissue and becomes a fibroepithelial crescent. This process generally results in glomerular obsolescence and the clinical development of chronic renal failure. Crescent formation is often associated with glomerular cell death. The necrotic glomerulus has a characteristic eosinophilic appearance and usually contains nuclear remnants. Crescent formation is usually associated with generalized proliferation of the mesangial cells and with either immune complex or anti-GBM antibody deposition in the glomerular capillary wall.

Certain forms of acute glomerulonephritis show glomerular exudation of blood cells, including neutrophils, eosinophils, basophils, and mononuclear cells. The thickened appearance of GBM can result from a true increase in the width of the membrane (as seen in membranous glomerulopathy; see Chapter 559.5), from massive deposition of immune complexes that have staining characteristics similar to the membrane (as seen in systemic lupus erythematosus; see Chapter 560.2), or from the interposition of mesangial cells and matrix into the subendothelial space between the endothelial cells and the GBM. The last can give the basement membrane a split appearance, as seen in membranoproliferative glomerulonephritis (see Chapter 559.6) and other diseases.

Sclerosis refers to obliteration of capillary loops within the glomerulus caused by increased mesangial matrix. Glomerulosclerosis may be caused by a putative circulating factor, as occurs in primary focal segmental glomerulosclerosis (FSGS), or it may be secondary to a variety of conditions including pathogenic variants, obesity, infection, certain medications, or any condition that results in reduced renal mass.

Tubulointerstitial fibrosis is present in all patients who have glomerular disease and who develop progressive renal injury. This fibrosis is initiated by injury to either the glomeruli, which, if severe, may secondarily involve the tubules, or direct injury to the tubules themselves. Tubular injury recruits mononuclear cell infiltrate, which releases a variety of soluble factors that have fibrosis-promoting effects. Matrix proteins of the renal interstitium begin to accumulate, leading to eventual destruction of renal tubules and peritubular capillaries.

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Section 2

Conditions Particularly Associated with Hematuria

Chapter 558

Clinical Evaluation of the Child with Hematuria

Francisco X. Flores

Hematuria, defined as the persistent presence of more than five red blood cells (RBCs)/high-power field (hpf) in uncentrifuged urine, occurs in 4–6% of urine samples from school-aged children. Quantitative studies demonstrate that normal children can excrete more than 500,000 RBCs per 12-hour period; this increases with fever and/or exercise. In the clinical setting, qualitative estimates are provided by a urinary dipstick that uses a very sensitive peroxidase chemical reaction between hemoglobin (or myoglobin) and a colorimetric chemical indicator impregnated on the dipstick. Chemstrip (Boehringer Mannheim), a common commercially available dipstick, is very sensitive and capable of detecting 3-5 RBCs/hpf of unspun urine. The presence of 10-50 RBCs/μL may suggest underlying pathology, but significant hematuria is generally considered as >50 RBCs/hpf. False-negative results can occur in the presence of formalin (used as a urine preservative) or high urinary concentrations of ascorbic acid (i.e., in patients with vitamin C intake >2,000 mg/day). False-positive results may be seen in a child with an alkaline urine (pH >8), or more commonly following contamination with oxidizing agents such as hydrogen peroxide used to clean the perineum before obtaining a specimen. Microscopic analysis of 10-15 mL of freshly voided and centrifuged urine is essential in confirming the presence of RBCs suggested by >10 RBCs/hpf, or a 1+ positive urinary dipstick reading.

Red urine *without* RBCs is seen in a number of conditions (Table 558.1). Clinically significant heme-positive urine without RBCs may be caused by the presence of either hemoglobin or myoglobin. **Hemoglobinuria** without hematuria can occur in the presence of acute or chronic hemolysis. **Myoglobinuria** without hematuria occurs in the presence of rhabdomyolysis resulting from skeletal muscle injury and is generally associated with a fivefold increase in the plasma concentration of creatine kinase. Clinically innocuous heme-negative urine can appear red, cola colored, or burgundy, due to ingestion of various drugs, foods (blackberries, beets), or dyes used in food and candy, whereas dark brown (or black) urine can result from various urinary metabolites.

Evaluation of the child with hematuria begins with a careful history, physical examination, and microscopic urinalysis. This information is used to determine the level of hematuria (upper vs lower urinary tract) and to determine the urgency of the evaluation based on symptomatology. Special consideration needs to be given to the family history, identification of anatomic abnormalities and malformation syndromes, presence of gross hematuria, and manifestations of hypertension, edema, or heart failure.

Table 558.2 lists causes of hematuria. Upper urinary tract sources of hematuria originate within the nephron (glomerulus, tubular system, or interstitium). Lower urinary tract sources of hematuria originate from the pelvicalyceal system, ureter, bladder, or urethra. Hematuria from within the glomerulus is often associated with brown, cola- or tea-colored, or burgundy urine, proteinuria >100 mg/dL via dipstick, urinary microscopic findings of RBC casts, and deformed urinary RBCs (particularly acanthocytes). Hematuria originating within the tubular system may be associated with the presence of leukocytes or renal tubular casts. Lower urinary tract sources of hematuria may be associated with gross hematuria that is bright red or pink, terminal hematuria (gross hematuria occurring at the end of the urine stream), blood clots, normal urinary RBC morphology, and minimal proteinuria on dipstick (<100 mg/dL).

Patients with hematuria can present with a number of symptoms suggesting specific disorders. Tea- or cola-colored urine, facial or body edema, hypertension, and oliguria are classic symptoms of **glomerulonephritis.** Diseases commonly manifesting as glomerulonephritis include postinfectious glomerulonephritis, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis (MPGN), IgA vasculitis nephritis (formerly Henoch-Schönlein purpura nephritis), systemic lupus erythematosus (SLE) nephritis, granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyangiitis, Goodpasture syndrome, and hemolytic-uremic syndrome. A history of recent upper respiratory, skin, or gastrointestinal infection suggests postinfectious glomerulonephritis, hemolytic-uremic syndrome, or IgA vasculitis nephritis. Rash and joint complaints suggest IgA vasculitis or SLE nephritis.

Hematuria associated with glomerulonephritis is typically painless but can be associated with flank pain when acute or unusually severe. Frequency, dysuria, and unexplained fevers suggest a urinary tract infection, whereas renal colic suggests nephrolithiasis. A flank mass can suggest hydronephrosis, renal cystic diseases, renal vein thrombosis, or tumor. Hematuria associated with headache, mental status changes, visual changes (diplopia), epistaxis, or heart failure suggests associated severe hypertension. Patients with hematuria and a history of trauma require immediate evaluation (see Chapter 80). Child abuse must always be suspected in the child presenting with unexplained perineal bruising and hematuria.

A careful family history is critical in the initial assessment of the child with hematuria given the numerous genetic causes of renal disorders. Hereditary glomerular diseases include hereditary nephritis (isolated Alport syndrome or with leiomyomatosis or macrothrombocytopenia); thin glomerular basement membrane disease; SLE nephritis; hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC); and IgA nephropathy (Berger disease). Other hematuric renal disorders with a hereditary component include both autosomal recessive and autosomal dominant polycystic kidney diseases, atypical hemolytic-uremic syndrome, urolithiasis, and sickle cell disease/trait.

Physical examination may also suggest possible causes of hematuria. The presence of hypertension, edema, or signs of heart failure suggests acute glomerulonephritis. Several malformation syndromes are associated with renal disease, including VATER (*v*ertebral body anomalies, *a*nal atresia, *t*racheo*e*sophageal fistula, and *r*enal dysplasia) syndrome. Abdominal masses may be caused by bladder distention in posterior urethral valves, hydronephrosis in ureteropelvic or ureterovesical junction obstruction, polycystic kidney disease, or Wilms tumor. Hematuria seen in patients with neurologic or cutaneous abnormalities may be the result of a number of syndromic renal disorders, including tuberous sclerosis, von Hippel-Lindau syndrome, and Zellweger (cerebrohepatorenal) syndrome. Anatomic abnormalities of the external genitalia may be associated with hematuria and/or renal disease.

Patients with gross hematuria present additional challenges because of the associated parental anxiety. The most common cause of gross hematuria is bacterial or viral urinary tract infection. **Urethrorrhagia,** which is urethral bleeding in the absence of urine, is associated with

Table 558.1 Other Causes of Red Urine

HEME POSITIVE
Hemoglobin
Myoglobin
HEME NEGATIVE
Drugs
Adriamycin
Chloroquine
Deferoxamine
Hydroxocobalamin
Ibuprofen
Iron sorbitol
Levodopa
Metronidazole
Nitrofurantoin
Phenazopyridine (Pyridium)
Phenolphthalein
Phenothiazines
Phenytoin
Quinine
Rifampin
Salicylates
Sulfasalazine
Dyes (Vegetable/Fruit)
Beets
Blackberries
Blueberries
Food and candy coloring
Paprika
Rhubarb
Metabolites
Homogentisic acid
Melanin
Methemoglobin
Porphyrin
Tyrosinosis
Urates

Table 558.2 Causes of Hematuria in Children

UPPER URINARY TRACT DISEASE
Isolated Renal Disease
Immunoglobulin (Ig) A nephropathy (Berger disease)
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane nephropathy
Postinfectious GN (poststreptococcal GN)*
Membranous nephropathy
Membranoproliferative GN*
Rapidly progressive GN
Focal segmental glomerulosclerosis
Anti–glomerular basement membrane disease
Hereditary angiopathy with nephropathy, aneurysms, muscle cramps (HANAC)
Multisystem Disease
Systemic lupus erythematosus nephritis*
IgA vasculitis nephritis†
Granulomatosis with polyangiitis‡
Microscopic polyangiitis
Goodpasture syndrome
Hemolytic-uremic syndrome
Sickle cell glomerulopathy
HIV nephropathy
Tubulointerstitial Disease
Pyelonephritis
Interstitial nephritis
Papillary necrosis
Acute tubular necrosis
Vascular Disorders
Arterial or venous thrombosis
Malformations (aneurysms, hemangiomas)
Nutcracker syndrome
Hemoglobinopathy (sickle cell trait/disease)
Crystalluria
Anatomic Disorders
Hydronephrosis
Cystic-syndromic kidney disease
Polycystic kidney disease
Multicystic dysplasia
Tumor (Wilms tumor, rhabdomyosarcoma, angiomyolipoma, medullary carcinoma)
Trauma
LOWER URINARY TRACT DISEASE
Inflammation (infectious and noninfectious)
Cystitis
Urethritis
Urolithiasis
Trauma
Coagulopathy
Heavy exercise
Bladder tumor
Factitious syndrome, factitious syndrome by proxy§

*Denotes glomerulonephritides presenting with hypocomplementemia.
†Formerly Henoch-Schönlein purpura.
‡Formerly Wegener granulomatosis.
§Formerly Munchausen syndrome and Munchausen syndrome by proxy.
GN, Glomerulonephritis.

dysuria and blood spots on underwear after voiding. This condition, which often occurs in prepubertal boys at intervals several months apart, has a benign self-limited course. Less than 10% of patients have evidence of glomerulonephritis. Recurrent episodes of gross hematuria suggest IgA nephropathy, Alport syndrome, or thin glomerular basement membrane disease. Dysuria and abdominal or flank pain are symptoms of idiopathic hypercalciuria, or urolithiasis. Table 558.3 lists common causes of gross hematuria; Figure 558.1 outlines a general approach to the laboratory and radiologic evaluation of the patient with glomerular or nonglomerular hematuria. Asymptomatic patients with isolated microscopic hematuria should not undergo extensive diagnostic evaluation, because such hematuria is often transient and benign.

The child with completely asymptomatic isolated microscopic hematuria that persists on at least three urinalyses observed over a minimum of a 2-week period poses a dilemma in regard to the degree of further diagnostic testing that should be performed. Significant disease of the urinary tract is uncommon with this clinical presentation. The initial evaluation of these children should include a urine culture followed by a spot urine for hypercalciuria with a calcium:creatinine ratio in culture-negative patients. In Black patients, a sickle cell screen should be included. If these studies are normal, urinalysis of all first-degree relatives is indicated. Renal and bladder ultrasonography should be considered to rule out structural lesions such as tumor, cystic disease, hydronephrosis, or urolithiasis. Ultrasonography of the urinary tract is most informative in patients presenting with gross hematuria, abdominal pain, flank pain, or trauma. If these initial studies are normal, assessment of serum creatinine and electrolytes is recommended.

The finding of certain hematologic abnormalities can narrow the differential diagnosis. **Anemia** in this setting may be caused by

Table 558.3 Common Causes of Gross Hematuria

Urinary tract infection
Meatal stenosis with ulcer
Perineal irritation
Trauma
Urolithiasis
Hypercalciuria
Obstruction
Coagulopathy
Tumor
Glomerular disease
Postinfectious glomerulonephritis
IgA vasculitis nephritis*
IgA nephropathy
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane disease
Systemic lupus erythematosus nephritis

*Formerly Henoch-Schönlein purpura.

hypervolemia with dilution associated with acute kidney injury; decreased RBC production in chronic kidney disease; hemolysis from hemolytic-uremic syndrome, a chronic hemolytic anemia, or SLE; blood loss from pulmonary hemorrhage, as seen in Goodpasture syndrome; or melena in patients with IgA vasculitis or hemolytic-uremic syndrome. Inspection of the peripheral blood smear might reveal a **microangiopathic** process consistent with the hemolytic-uremic syndrome. The presence of autoantibodies in SLE can result in a positive Coombs test, the presence of antinuclear antibody, leukopenia, and multisystem disease. **Thrombocytopenia** can result from decreased platelet production (malignancies) or increased platelet consumption (SLE, idiopathic thrombocytopenic purpura, hemolytic-uremic syndrome, renal vein thrombosis, or congenital hepatic fibrosis with portal hypertension secondary to autosomal recessive polycystic kidney disease). Although urinary RBC morphology may be normal with lower tract bleeding and dysmorphic from glomerular bleeding, it is not sensitive enough to unequivocally delineate the site of hematuria. A bleeding diathesis is an unusual cause of hematuria, and coagulation studies are not routinely obtained unless a personal or family history suggests a bleeding tendency.

A voiding cystourethrogram is only required in patients with a urinary tract infection, renal scarring, hydroureter, or pyelocaliectasis. Cystoscopy is an unnecessary and costly procedure in most pediatric patients with hematuria and carries the associated risks of anesthesia. This procedure should be reserved for evaluating the rare child with a bladder mass noted on ultrasound, urethral abnormalities caused by trauma, posterior urethral valves, or tumor. The finding of unilateral gross hematuria localized by cystoscopy is rare, but it can indicate a vascular malformation or another anatomic abnormality.

Children with persistent asymptomatic isolated hematuria and a completely normal evaluation should have their blood pressure and urine checked every 3 months until the hematuria resolves. Referral to a pediatric nephrologist should be considered for patients with persistent asymptomatic hematuria greater than 1 year in duration and is recommended for patients with nephritis (glomerulonephritis, tubulointerstitial nephritis), hypertension, renal dysfunction, urolithiasis or nephrocalcinosis, or a family history of renal disease such as polycystic kidney disease or hereditary nephritis. Renal biopsy is indicated for some children with persistent microscopic hematuria and for most children with recurrent gross hematuria associated with decreased renal function, proteinuria, or hypertension.

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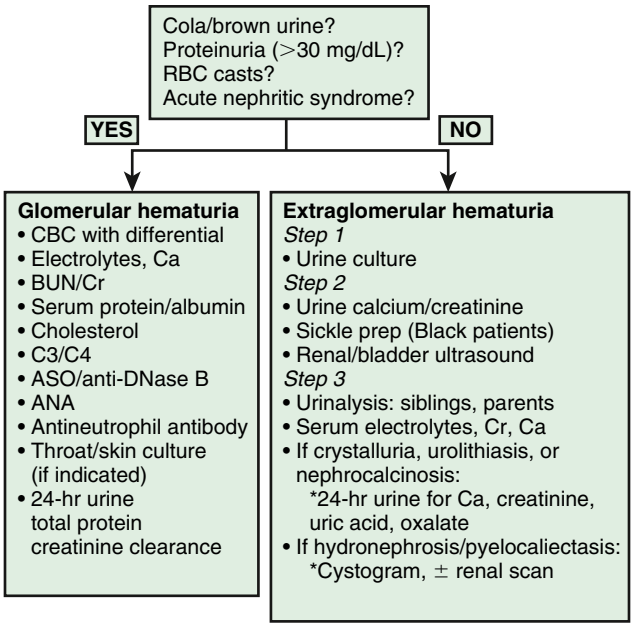

Fig. 558.1 Diagnostic algorithm of the general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. ANA, Antinuclear antibody; ASO, antistreptolysin O; BUN, blood urea nitrogen; C3/C4, complement; CBC, complete blood cell count; Cr, creatinine; RBC, red blood cell.

Chapter 559

Isolated Glomerular Diseases Associated with Recurrent Gross Hematuria

Francisco X. Flores

INTRODUCTION

Approximately 10% of children with gross hematuria have an acute or a chronic form of glomerulonephritis that may be associated with a systemic illness. The gross hematuria, which is usually characterized by brown or cola-colored urine, may be painless or associated with vague flank or abdominal pain. A presentation with gross hematuria is common within 1-2 days after the onset of an apparent viral upper respiratory tract infection in immunoglobulin (Ig) A nephropathy and typically resolves within 5 days. This relatively short period contrasts with a latency period of 7-21 days occurring between the onset of a streptococcal pharyngitis or impetiginous skin infection and the development of postinfectious acute glomerulonephritis. Gross hematuria in these circumstances can last as long as 4-6 weeks. Gross hematuria can also be seen in children with glomerular basement membrane (GBM) disorders such as hereditary nephritis (Alport syndrome [AS]) and thin GBM disease. These glomerular diseases can also manifest as microscopic hematuria and/or proteinuria without gross hematuria.

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559.1 Immunoglobulin A Nephropathy (Berger Nephropathy)

Francisco X. Flores

IgA nephropathy is the most common chronic glomerular disease in children. It is characterized by a predominance of IgA within mesangial glomerular deposits in the absence of systemic disease. Its diagnosis requires a renal biopsy, which is performed when clinical features warrant confirmation of the diagnosis or characterization of the histologic severity, which might affect therapeutic decisions.

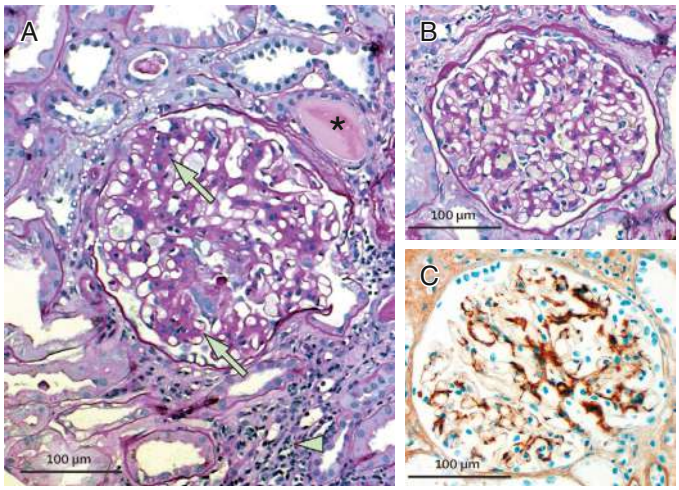

Fig. 559.1 IgA nephropathy. **A,** In IgA nephropathy, segmental areas *(arrows)* of mesangial hypercellularity and matrix expansion occur, characteristic of mesangioproliferative glomerulonephritis. Part of the glomerular tuft adheres to Bowman's capsule *(white dashed oval)*, constituting the starting point of a secondary focal segmental glomerulosclerosis lesion. Tubulointerstitial damage with leukocyte infiltrates, tubular atrophy and fibrosis *(arrowhead)*, and tubular protein casts *(asterisk)* is also present. Periodic acid–Schiff (PAS) stain. **B,** Other glomeruli in the same patient exhibit few pathologic abnormalities on light microscopy (PAS stain), but the characteristic mesangial granular IgA deposition (**C**) can be found in these glomeruli as well. *(From Floege J, Amann K. Primary glomerulonephritides. Lancet. 2016;387:2036–2046. Fig. 2.)*

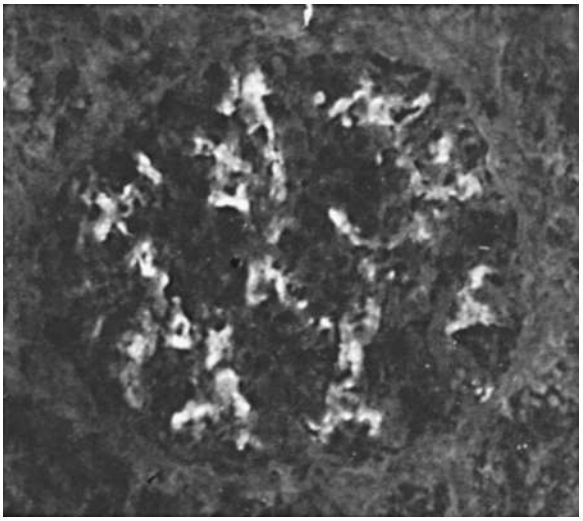

Fig. 559.2 Immunofluorescence microscopy of the biopsy specimen from a child with episodes of gross hematuria demonstrating mesangial deposition of IgA (×150).

PATHOLOGY AND PATHOLOGIC DIAGNOSIS

Focal and segmental mesangial proliferation and an increased mesangial matrix are seen in the glomerulus (Fig. 559.1). Renal histology demonstrates mesangial proliferation that may be associated with epithelial cell crescent formation and sclerosis. IgA deposits in the mesangium are often accompanied by C3 complement (Fig. 559.2).

IgA nephropathy is an immune complex disease initiated by excessive amounts of poorly galactosylated IgA_1 in the serum, causing the production of IgG and IgA autoantibodies. The abnormalities identified in the IgA system have also been observed in patients with IgA vasculitis (formerly known as Henoch-Schönlein purpura), and this finding lends support to the hypothesis that these two diseases are part of the same disease spectrum. Familial clustering of IgA nephropathy cases suggests the importance of genetic factors. Genome-wide linkage analysis suggests the linkage of IgA nephropathy to 6q22-23 in multiplex IgA nephropathy kindreds. Additional genomic studies demonstrate a high predisposition to IgA nephropathy in Southeast Asia.

CLINICAL AND LABORATORY MANIFESTATIONS

IgA nephropathy is seen more often in male than in female patients. Although there are rare cases of rapidly progressive forms of the disease, the clinical presentation of childhood IgA nephropathy is often benign compared with that of adults. IgA nephropathy is an uncommon cause of end-stage renal failure during childhood. A majority of children with IgA nephropathy in the United States and Europe present with gross hematuria, whereas microscopic hematuria and/or proteinuria is a more common presentation in Japan. Other presentations include acute nephritic syndrome, nephrotic syndrome, or a combined nephritic-nephrotic picture. Gross hematuria often occurs within 1-2 days of onset of an upper respiratory or gastrointestinal infection, in contrast with the longer latency period observed in acute postinfectious glomerulonephritis and may be associated with loin pain. Proteinuria is often <1,000 mg/24 hr in patients with asymptomatic microscopic hematuria. Mild to moderate hypertension is most often seen in patients with nephritic or nephrotic syndrome but is rarely severe enough to result in hypertensive emergencies. Normal serum levels of C3 in IgA nephropathy help to distinguish this disorder from postinfectious glomerulonephritis. Serum IgA levels have limited diagnostic value because they are elevated in only 50% of pediatric patients.

PROGNOSIS AND TREATMENT

Although IgA nephropathy does not lead to significant kidney damage in most children, progressive disease develops in 20–30% of adult patients 15-20 years after disease onset. Therefore most children with IgA nephropathy do not display progressive renal dysfunction until adulthood, prompting the need for careful long-term follow-up. Poor

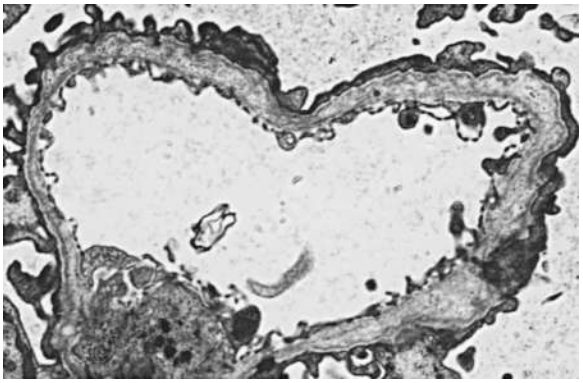

Fig. 559.3 Electron micrograph of a biopsy specimen from a child with Alport syndrome depicting thickening, thinning, splitting, and layering of the glomerular basement membrane (GBM; ×1,650). *(From Yum M, Bergstein JM. Basement membrane nephropathy. Hum Pathol. 1983;14:996–1003.)*

prognostic indicators at presentation or follow-up include persistent hypertension, diminished renal function, and significant, increasing, or persistent proteinuria. A more severe prognosis is correlated with histologic evidence of diffuse mesangial proliferation, extensive glomerular crescents, glomerulosclerosis, and diffuse tubulointerstitial changes, including inflammation and fibrosis.

The primary treatment of IgA nephropathy is appropriate blood pressure control and management of significant proteinuria. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are effective in reducing proteinuria and slowing the rate of disease progression when used individually or in combination. Fish oil, which contains antiinflammatory omega-3 polyunsaturated fatty acids, may decrease the rate of disease progression in adults. If a renin-angiotensin system (RAS) blockade proves ineffective and significant proteinuria persists, then addition of immunosuppressive therapy with corticosteroids is recommended. Corticosteroids reduce proteinuria and improve renal function in those patients with a glomerular filtration rate >60 mL/min/m^2. It remains unclear if the effects of glucocorticoids deter progression to end-stage renal failure to a degree to offset their significant side effects. Additional immunosuppression with cyclophosphamide or azathioprine has not appeared to be effective. Tonsillectomy has been used as a treatment for IgA nephropathy in many countries, including Japan. Performing a tonsillectomy in the absence of significant tonsillitis in association with IgA nephropathy is currently not recommended. Targeted-release oral budesonide is approved by the FDA to reduce proteinuria in adult patients with IgA nephropathy. Patients with IgA nephropathy may undergo successful kidney transplantation. Although recurrent disease is frequent, allograft loss caused by IgA nephropathy occurs in only 15–30% of patients.

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559.2 Alport Syndrome

Francisco X. Flores

Alport syndrome (AS), or hereditary nephritis, is a genetically heterogeneous disease caused by pathogenic variants in the genes coding for type IV collagen, a major component of basement membranes. These genetic alterations are associated with marked variability in the clinical presentation, natural history, and histologic abnormalities.

GENETICS

Approximately 70–80% of patients have X-linked inheritance caused by a mutation in the *COL4A5* gene encoding the α5 chain of type IV collagen. Patients with a subtype of X-linked AS and diffuse **leiomyomatosis** demonstrate a contiguous pathogenic variant within the *COL4A5* and *COL4A6* genes that encodes the α5 and α6 chains, respectively, of type IV collagen. Autosomal recessive forms of AS in approximately 5% of patients are caused by pathogenic variants in the *COL4A3* and *COL4A4* genes on chromosome 2 encoding the α3 and α4 chains, respectively, of type IV collagen. An autosomal dominant form of AS linked to the *COL4A3-COL4A4* gene locus occurs in 19–31% of cases.

Fechtner syndrome (AS with macrothrombocytopenia) and **Epstein syndrome** are autosomal dominant disorders due to pathogenic variants in *MYH9*. **Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC)** may initially resemble AS. HANAC is due to pathogenic variants in the *COL4A1* gene.

PATHOLOGY

Kidney biopsy specimens during the first decade of life will show only a few changes on light microscopy. Later, the glomeruli may develop mesangial proliferation and capillary wall thickening, leading to progressive glomerular sclerosis. Tubular atrophy, interstitial inflammation and fibrosis, and lipid-containing tubular or interstitial cells, called *foam cells,* develop as the disease progresses. Immunopathologic studies are usually nondiagnostic.

In most patients, electron microscopy reveals diffuse thickening, thinning, splitting, and layering of the glomerular and tubular basement membranes (Fig. 559.3). To confound the diagnosis, the ultrastructural analysis of the GBM in all genetic forms of AS may be completely normal, display nonspecific alterations, or demonstrate only uniform thinning.

CLINICAL MANIFESTATIONS

All patients with AS have *asymptomatic* microscopic hematuria, which may be *intermittent* in females and younger males. Single or recurrent episodes of gross hematuria commonly occurring 1-2 days after an upper respiratory infection are seen in approximately 50% of patients. Proteinuria is often seen in males but may be absent, mild, or intermittent in females. Progressive proteinuria, often exceeding 1 g/24 hours, is common by the second decade of life and can be severe enough to cause nephrotic syndrome.

Bilateral **sensorineural hearing loss,** which is never congenital, develops in 90% of hemizygous males with X-linked AS, 20% of heterozygous females with X-linked AS, and 67% of patients with autosomal recessive AS. This deficit begins in the high-frequency range but progresses to involve the hearing associated with normal speech, prompting the need for hearing aids. This progression of hearing loss seems to run parallel to the loss of renal function. **Ocular abnormalities**, which occur in 30–40% of patients with X-linked AS, include anterior lenticonus (extrusion of the central portion of the lens into the anterior chamber), macular flecks, and corneal erosions. **Leiomyomatosis** of the esophagus, tracheobronchial tree, and female genitals has been reported but is rare.

DIAGNOSIS

A combination of a thorough family history, a screening urinalysis of first-degree relatives, an audiogram, and an ophthalmologic examination are critical in making the diagnosis of AS. The presence of anterior lenticonus is pathognomonic. AS is highly likely in the patient who has hematuria and at least two of the following characteristic clinical features: macular flecks, recurrent corneal erosions, GBM thickening and thinning, or sensorineural deafness. The absence of epidermal basement membrane staining for the α5 chain of type IV collagen in male hemizygotes and discontinuous epidermal basement membrane staining in female heterozygotes on skin biopsy is pathognomonic for X-linked AS and can preclude a diagnostic renal biopsy. Genetic testing is clinically available for X-linked AS and *COL4A5* pathogenic variants. Prenatal diagnosis is available for families with members who have X-linked AS and who carry an identified pathogenic variant.

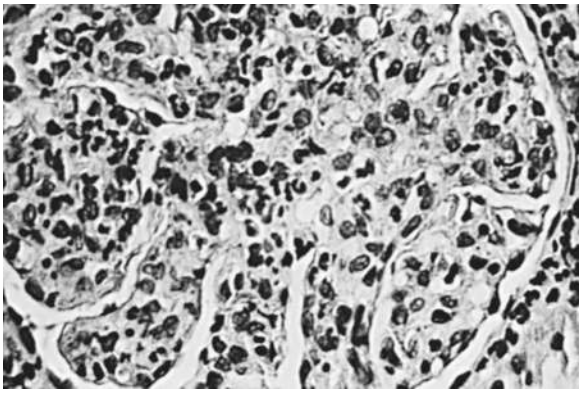

Fig. 559.4 Glomerulus from a patient with poststreptococcal glomerulonephritis appears enlarged and relatively bloodless and shows mesangial proliferation and exudation of neutrophils (×400).

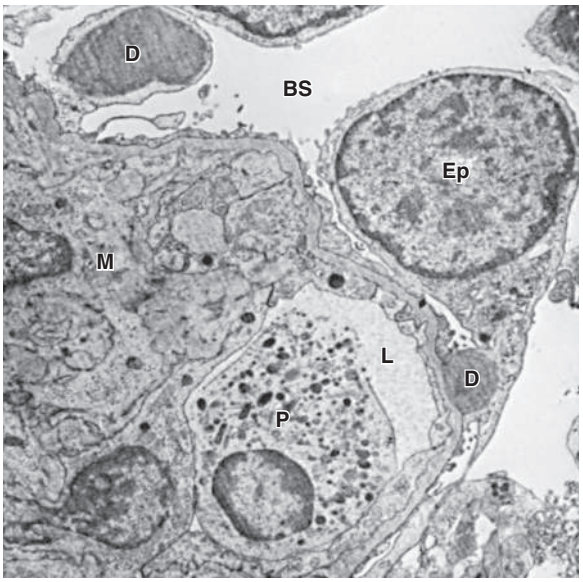

Fig. 559.5 Electron micrograph in poststreptococcal glomerulonephritis demonstrating electron-dense deposits *(D)* on the epithelial cell *(Ep)* side of the glomerular basement membrane. A polymorphonuclear leukocyte *(P)* is present within the lumen *(L)* of the capillary. BS, Bowman's space; M, mesangium.

PROGNOSIS AND TREATMENT

The risk of progressive renal dysfunction leading to end-stage kidney disease (ESKD) is highest among hemizygotes and autosomal recessive homozygotes. ESKD occurs before age 30 years in approximately 75% of hemizygotes with X-linked AS. The risk of ESKD in X-linked heterozygotes is 12% by age 40 years and 30% by age 60 years. Risk factors for progression are gross hematuria during childhood, nephrotic syndrome, and prominent GBM thickening. An intrafamilial variation in phenotypic expression results in significant differences in the age of ESKD among family members. No specific therapy is available to treat AS, although angiotensin-converting enzyme inhibitors (and possibly angiotensin II receptor inhibitors) can slow the rate of progression. Careful management of renal failure complications, such as hypertension, anemia, and electrolyte imbalance, is critical. Patients with ESKD are treated with dialysis and kidney transplantation (see Chapter 573). Approximately 5% of kidney transplantation recipients develop anti-GBM nephritis, which occurs primarily in males with X-linked AS who develop ESKD before age 30 years.

Pharmacologic treatment of proteinuria with angiotensin-converting enzyme inhibition or angiotensin II receptor blockade has proven effective in other glomerular diseases and has also shown promise in AS. Screening of heterozygote carriers for significant renal disease in later adulthood and possible treatment of significant proteinuria is also recommended.

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559.3 Thin Basement Membrane Disease

Francisco X. Flores

Thin basement membrane disease (TBMD) is defined by the presence of persistent microscopic hematuria and isolated thinning of the GBM (and, occasionally, tubular basement membranes) on electron microscopy. Microscopic hematuria is often initially observed during childhood and may be intermittent. Episodic gross hematuria can also be present, particularly after a respiratory illness. Isolated hematuria in multiple family members without renal dysfunction is referred to as **benign familial hematuria.** Although most of these patients will not undergo renal biopsy, it is often presumed that the underlying pathology is TBMD. TBMD may be sporadic or transmitted as an autosomal dominant trait. Heterozygous pathogenic variants in the *COL4A3* and *COL4A4* genes, which encode the α3 and α4 chains of type IV collagen present in the GBM, result in TBMD. Rare cases of TBMD progress, and such patients develop significant proteinuria, hypertension, or renal insufficiency. Homozygous pathogenic variants in these same genes result in autosomal recessive AS. Therefore in these rare cases, the absence of a positive family history for renal insufficiency or deafness would not necessarily predict a benign outcome. Consequently, monitoring patients with benign familial hematuria for progressive proteinuria, hypertension, or renal dysfunction is important throughout childhood and young adulthood.

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559.4 Acute Poststreptococcal Glomerulonephritis

Francisco X. Flores

Group A β-hemolytic streptococcal infections are common in children and can lead to the postinfectious complication of acute GN. Acute poststreptococcal glomerulonephritis (APSGN) is a classic example of the **acute nephritic syndrome** characterized by the sudden onset of gross hematuria, edema, hypertension, and renal dysfunction. It is one of the most common glomerular causes of gross hematuria in children and is a major cause of morbidity in group A β-hemolytic streptococcal infections.

ETIOLOGY AND EPIDEMIOLOGY

APSGN follows infection of the throat or skin by certain *nephritogenic* strains of group A β-hemolytic streptococci. Epidemics and clusters of household (camps, military) cases occur throughout the world, and 97% of cases occur in less-developed countries. The overall incidence has decreased in industrialized nations, presumably as a result of improved hygienic conditions and the near eradication of streptococcal pyoderma. Poststreptococcal GN commonly follows streptococcal pharyngitis during cold-weather months and streptococcal skin infections or pyoderma during warm-weather months. Although epidemics of nephritis have been described in association with throat (serotypes M1, M4, M25, and some strains of M12) and skin (serotype M49) infections, this disease is most commonly sporadic.

PATHOLOGY

Glomeruli appear enlarged and relatively bloodless and show a diffuse mesangial cell proliferation, with an increase in mesangial matrix (Fig. 559.4). Polymorphonuclear leukocyte infiltration is common in glomeruli during the early stage of the disease. Crescents and interstitial inflammation may be seen in severe cases, but these changes are not specific for poststreptococcal GN. Immunofluorescence microscopy reveals a pattern of "lumpy-bumpy" deposits of immunoglobulin and complement on the glomerular basement membrane and in the mesangium. On electron microscopy, electron-dense deposits, or "humps," are observed on the epithelial side of the glomerular basement membrane (Fig. 559.5).

PATHOGENESIS

Morphologic studies and a depression in the serum complement (C3) level provide strong evidence that ASPGN is mediated by immune complexes. Circulating immune complex formation with streptococcal antigens and subsequent glomerular deposition is thought less likely to be a pathogenic mechanism. Molecular mimicry, whereby circulating antibodies elicited by streptococcal antigens react with normal glomerular antigens, in situ immune complex formation of antistreptococcal

Table 559.1 Summary of Primary Renal Diseases that Manifest as Acute Glomerulonephritis

DISEASES	POSTSTREPTOCOCCAL GLOMERULONEPHRITIS	IGA NEPHROPATHY	GOODPASTURE SYNDROME	IDIOPATHIC RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS
CLINICAL MANIFESTATIONS				
Age and sex	All ages, mean 7 yr, 2:1 male	10-35 yr, 2:1 male	15-30 yr, 6:1 male	Adults, 2:1 male
Acute nephritic syndrome	90%	50%	90%	90%
Asymptomatic hematuria	Occasionally	50%	Rare	Rare
Nephrotic syndrome	5–10%	Rare	Rare	10–20%
Hypertension	60%	30–50%	Rare	25%
Acute renal failure	50% (transient)	Very rare	50%	60%
Other	Latent period of 1-3 wk	Follows viral syndromes	Pulmonary hemorrhage; iron deficiency anemia	None
Laboratory findings	↑ ASO titers (70%) Positive Streptozyme (95%) ↓ C3-C9; normal C1, C4	↑ Serum IgA (50%) IgA in dermal capillaries	Positive anti-GBM antibody	Positive ANCA in some
Immunogenetics	HLA-B12, D "EN" (9)*	HLA-Bw 35, DR4 (4)*	HLA-DR2 (16)*	None established
RENAL PATHOLOGY				
Light microscopy	Diffuse proliferation	Focal proliferation	Focal → diffuse proliferation with crescents	Crescentic GN
Immunofluorescence	Granular IgG, C3	Diffuse mesangial IgA	Linear IgG, C3	No immune deposits
Electron microscopy	Subepithelial humps	Mesangial deposits	No deposits	No deposits
Prognosis	95% resolve spontaneously 5% RPGN or slowly progressive	Slow progression in 25–50%	75% stabilize or improve if treated early	75% stabilize or improve if treated early
Treatment	Monitor for oliguria, hypertension; treat appropriately	Uncertain (options include steroids, and ACE inhibitors); sparsentan (adults)	Plasma exchange, steroids, cyclophosphamide	Steroid pulse therapy

*Relative risk.
ACE, Angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin O; GBM, glomerular basement membrane; GN, glomerulonephritis; HLA, human leukocyte antigen; Ig, immunoglobulin; RPGN, idiopathic rapidly progressive glomerulonephritis.
From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004.

antibodies with glomerular deposited antigen, and complement activation by directly deposited streptococcal antigens, continues to be considered as a probable mechanism of immunologic injury.

Group A streptococci possesses M proteins, and nephritogenic strains are related to the M protein serotype. The search for the precise nephritogenic antigen(s) that cause disease suggests that streptococcal pyogenic exotoxin (SPE) B and nephritis-associated streptococcal plasmin receptor are promising candidates. Both have been identified in glomeruli of affected patients, and in one study, circulating antibodies to SPE B were found in all patients. Cross reactivity of SPE B and other M proteins with various components of the glomerular basement membrane also give evidence for molecular mimicry.

CLINICAL MANIFESTATIONS

Poststreptococcal GN is most common in children ages 5-12 years and uncommon before the age of 3 years. The typical patient develops an acute nephritic syndrome 1-2 weeks after an antecedent streptococcal pharyngitis or 3-6 weeks after a streptococcal pyoderma. The history of a specific infection may be absent because symptoms may have been mild or have resolved without patients receiving specific treatment or seeking the care of a medical provider.

The severity of kidney involvement varies from asymptomatic microscopic hematuria with normal renal function to gross hematuria with acute renal failure. Depending on the severity of renal involvement, patients can develop various degrees of edema, hypertension, and oliguria. Patients are at risk for developing encephalopathy and/or heart failure secondary to hypertension or hypervolemia. Hypertensive encephalopathy must be considered in patients with blurred vision, severe headaches, altered mental status, or new seizures. The effects of acute hypertension not only depend on the severity of hypertension but also the absolute change in comparison with the patient's baseline blood pressure and the rate at which it has risen. Respiratory distress, orthopnea, and cough may be symptoms of pulmonary edema and heart failure. Peripheral edema typically results from salt and water retention and is common; nephrotic syndrome develops in a minority (<5%) of childhood cases. Atypical presentations of APSGN include those with subclinical disease and those with severe symptoms but an absence of initial urinary abnormalities; in individuals who present with a purpuric rash, it is difficult to distinguish APSGN from IgA vasculitis without a renal biopsy.

The acute phase generally resolves within 6-8 weeks. Although urinary protein excretion and hypertension usually normalize by 4-6 weeks after onset, persistent microscopic hematuria can persist for 1-2 years after the initial presentation.

DIAGNOSIS

Urinalysis demonstrates red blood cells, often in association with red blood cell casts, proteinuria, and polymorphonuclear leukocytes. A mild normochromic anemia may be present from hemodilution and low-grade hemolysis. The serum C3 level is significantly reduced in >90% of patients in the acute phase and returns to normal 8-10 weeks

Table 559.2 Secondary Causes of Membranoproliferative Glomerulonephritis

ASSOCIATED WITH INFECTION
Hepatitis B and C
Visceral abscesses
Infective endocarditis
Shunt nephritis
Quartan malaria
Schistosoma nephropathy
Mycoplasma infection
ASSOCIATED WITH RHEUMATOLOGIC DISEASE
Systemic lupus erythematosus
Scleroderma
Sjögren syndrome
Sarcoidosis
Mixed essential cryoglobulinemia with or without hepatitis C infection
Anti–smooth muscle syndrome
ASSOCIATED WITH MALIGNANCY
Carcinoma
Lymphoma
Leukemia
ASSOCIATED WITH AN INHERITED DISORDER
α_1-Antitrypsin deficiency
Complement deficiency (C2 or C3), with or without partial lipodystrophy

From Saha MK, Pendergraft WF III, Jennette JC, et al. Primary glomerular disease. In: Yu AS, Chertow GM, Luyckx VA, et al., eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Box 31.7.

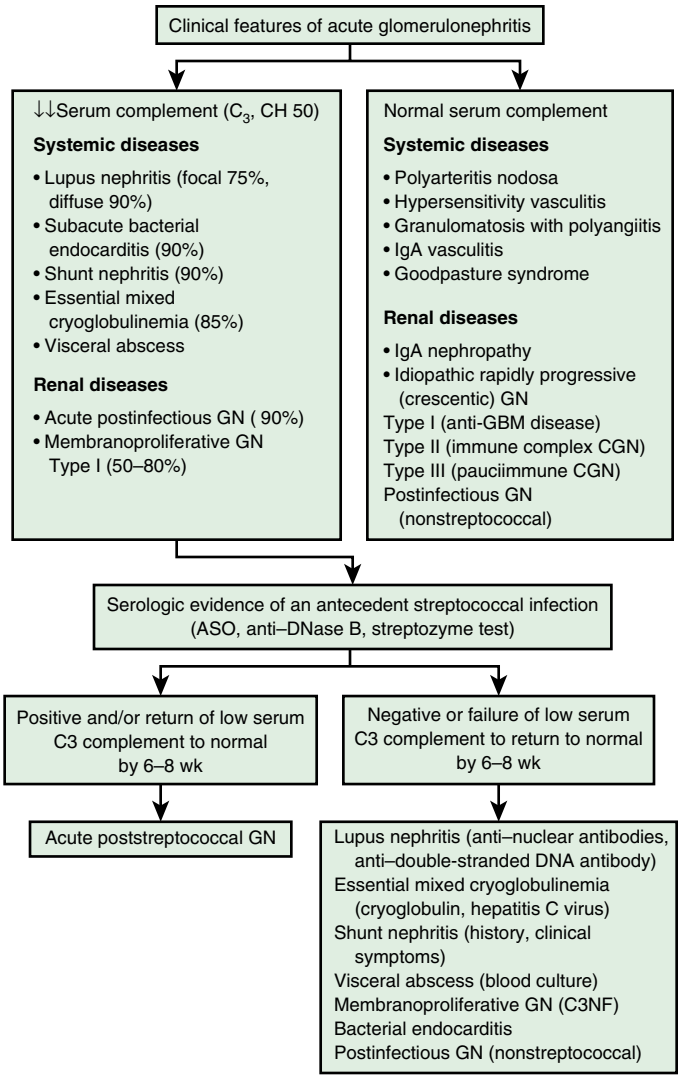

Fig. 559.6 Differential diagnostic algorithm of acute glomerulonephritis *(GN).* ASO, Anti–streptolysin O; CGN, crescentic glomerulonephritis; GBM, glomerular basement membrane; NF, nuclear factor. *(Adapted from Sulyok E. Acute proliferative glomerulonephritis. In: Avner ED, Harmon WE, Niaudet P, eds. Pediatric Nephrology, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2004: Fig. 30-4.)*

after the onset. Although serum CH_{50} is commonly depressed, *C4 is most often normal in APSGN,* or only mildly depressed.

Confirmation of the diagnosis requires clear evidence of a prior streptococcal infection. A positive throat culture report might support the diagnosis or might represent the carrier state. A rising antibody titer to streptococcal antigen(s) confirms a recent streptococcal infection. The antistreptolysin O titer is commonly elevated after a pharyngeal infection but rarely increases after streptococcal skin infections. The best single antibody titer to document cutaneous streptococcal infection is the antideoxyribonuclease B level. If available, a positive Streptozyme screen (which measures multiple antibodies to different streptococcal antigens) is a valuable diagnostic tool. Serologic evidence for streptococcal infections is more sensitive than the history of recent infections and far more sensitive than positive bacterial cultures obtained at the time of onset of acute nephritis.

MRI of the brain is indicated in patients with severe neurologic symptoms and can demonstrate **posterior reversible encephalopathy syndrome** in the parietooccipital areas on T2 weighted images. Chest x-ray is indicated in those with signs of heart failure or respiratory distress, or physical exam findings of a heart gallop, decreased breath sounds, rales, or hypoxemia.

The clinical diagnosis of poststreptococcal GN is quite likely in a child presenting with acute nephritic syndrome, evidence of recent streptococcal infection, and a low C3 level. However, it is important to consider other diagnoses such as systemic lupus erythematosus, endocarditis, membranoproliferative GN, and an acute exacerbation of chronic GN. Renal biopsy should be considered only in the presence of acute renal failure, nephrotic syndrome, absence of evidence of streptococcal infection, or normal complement levels. In addition, renal biopsy is considered when hematuria and proteinuria, diminished renal function, and/or a low C3 level persist more than 2 months after onset. Persistent hypocomplementemia can indicate a chronic form of postinfectious GN or another disease such as membranoproliferative GN.

The differential diagnosis of poststreptococcal GN includes many of the causes of hematuria listed in Table 559.1 and Table 558.2, and algorithms to help with the diagnosis are presented in Figs. 559.6 and 559.7. Acute postinfectious GN can also follow other infections with coagulase-positive and coagulase-negative staphylococci, *Streptococcus pneumoniae,* and gram-negative bacteria. The clinical course, histopathology, and laboratory features are similar to those described for APSGN. For some, the terms APSGN and acute postinfectious GN are used synonymously. Acute GN can occur after certain fungal, rickettsial, protozoan, parasitic, or viral diseases. Among the latter, influenza and parvovirus infections are particularly notable.

COMPLICATIONS

Acute complications result from hypertension and acute renal dysfunction. Hypertension is seen in 60% of patients and is associated with hypertensive encephalopathy in 10% of cases. Although the

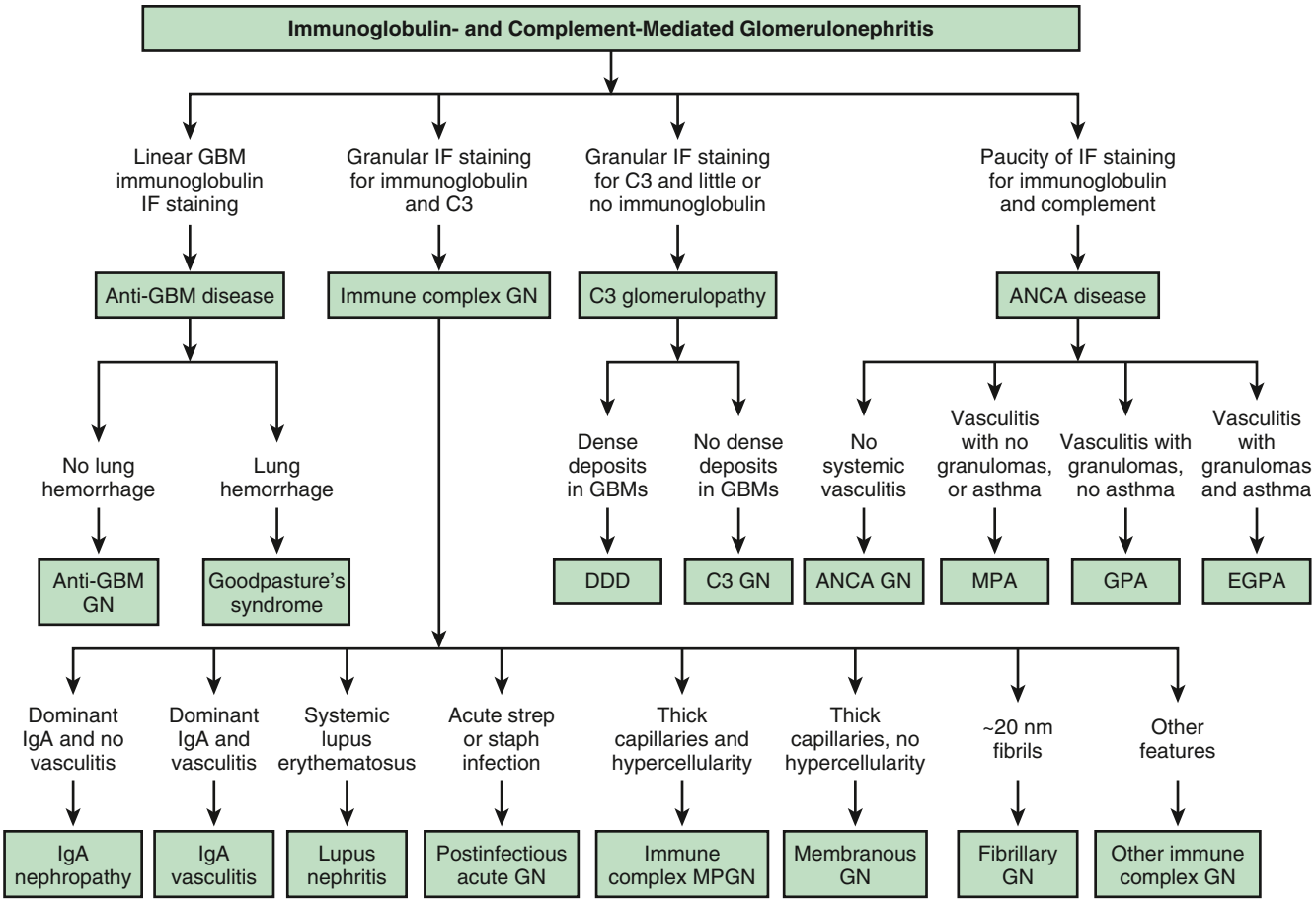

Fig. 559.7 Algorithm for diagnostic classification of glomerulonephritis *(GN)* that is known or suspected of being mediated by antibodies and complement. Note that the integration of light microscopy, immunofluorescence *(IF)* microscopy, electron microscopy, laboratory data, and clinical manifestations is required to precisely diagnose GN. ANCA, Anti–neutrophil cytoplasmic autoantibody; DDD, dense deposit disease; EGPA, eosinophilic granulomatosis with polyangiitis; GBM, glomerular basement membrane; GPA, granulomatosis with polyangiitis; IgA, immunoglobulin A; MPA, microscopic polyangiitis; MPGN, membranoproliferative glomerulonephritis. *(From Saha MK, Pendergraft WF III, Jennette JC, et al. Primary glomerular disease. In Yu AS, BChir GM, Chertow GM, et al., eds. Brenner & Rector's The Kidney, 11th ed. Philadelphia: Elsevier; 2020: Fig. 31-35.)*

neurologic sequelae are often reversible with appropriate management, severe prolonged hypertension can lead to intracranial bleeding. Other potential complications include heart failure, hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizures, and uremia. Acute renal failure can require treatment with dialysis.

PREVENTION

Early systemic antibiotic therapy for streptococcal throat and skin infections does not eliminate the risk of GN. Family members of patients with acute GN, especially young children, should be considered at risk and be cultured for group A β-hemolytic streptococci and treated if positive. Family pets, particularly dogs, have also been reported as carriers.

TREATMENT

Management is directed at treating the acute effects of renal dysfunction and hypertension (see Chapter 572.1). Although a 10-day course of systemic antibiotic therapy with penicillin is recommended to limit the spread of the nephritogenic organisms, antibiotic therapy does not affect the natural history of APSGN. This is unlike the GN seen in the context of ongoing or chronic infections, as noted in Chapter 560.1. Sodium and fluid restriction, diuretics, and pharmacotherapy with calcium channel antagonists, vasodilators, or angiotensin-converting enzyme inhibitors are standard therapies used to treat hypertension.

PROGNOSIS

Complete recovery occurs in >95% of children with APSGN. Recurrences are extremely rare. Mortality in the acute stage can be avoided by appropriate management of acute renal failure, cardiac failure, and hypertension. Infrequently, the acute phase is severe and leads to glomerulosclerosis and chronic renal disease in <2% of affected children.

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559.5 Membranous Nephropathy

Francisco X. Flores

Membranous nephropathy (MN), among the most common causes of nephrotic syndrome in adults, is a rare cause of nephrotic syndrome in children. MN is classified as the primary, idiopathic form, where there is isolated renal disease, or secondary MN, where nephropathy is associated with other identifiable systemic diseases or medications. In children, *secondary* MN is far more common than primary, idiopathic MN. The most common etiologies of secondary

MN are systemic lupus erythematosus or chronic infections. Among the latter, chronic hepatitis B infection and congenital syphilis are the best characterized and recognized causes of MN. Other chronic infections have also been associated with MN, including malaria, which is likely the most common cause of nephrotic syndrome worldwide. Certain medications, such as penicillamine and gold, or chronic factor replacement in patients with hemophilia, can also cause MN. Rare causes associated with MN include tumors, such as neuroblastoma, or other idiopathic systemic diseases. Identification of secondary causes of MN is critical, because removal of the offending agent or treatment of the causative disease often leads to resolution of the associated nephropathy and improves patient outcome.

PATHOLOGY

Glomeruli have diffuse thickening of the glomerular basement membrane (GBM), without significant cell proliferative changes. Immunofluorescence and electron microscopy typically demonstrate granular deposits of IgG and C3 located on the epithelial side of the GBM. The GBM thickening presumably results from the production of membrane-like material in response to deposition of immune complexes (Fig. 559.8).

PATHOGENESIS

MN is believed to be caused by in situ immune complex formation. Therefore antigens from the infectious agents or medications associated with secondary MN directly contribute to the pathogenesis of the renal disease. The causative antigen in idiopathic MN is not established, but the podocyte phospholipase A2 receptor (PLA2R), present on normal podocytes, may be a target antigen in idiopathic MN. Antigen from this receptor is found in immune deposits extracted from glomeruli in patients with idiopathic MN. The majority of idiopathic MN patients have circulating antibody against this podocyte membrane antigen, as well as against several podocyte cytoplasmic antigens. Childhood MN may be associated with anticationic bovine serum albumin antibodies. In addition, neutral endopeptidase antigen may be the antigen in neonatal onset MN.

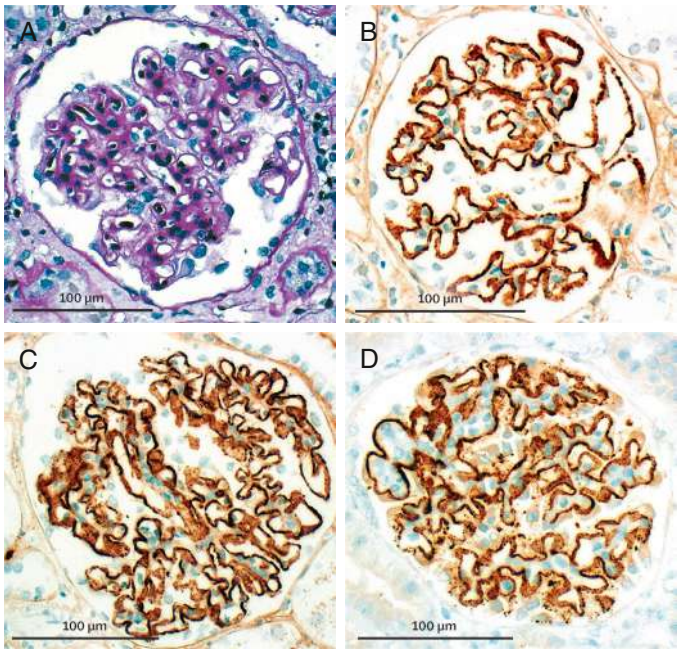

Fig. 559.8 Membranous glomerulonephritis. The periodic acid–Schiff (PAS) stain (A) shows slightly thickened glomerular basement membranes and prominent podocytes. On immunohistology, granular deposits of IgG (B) and C3c (C) can be found along the glomerular basement membrane, and pronounced de novo expression of phospholipase A2 receptor (PLA2R) (D) is present on the podocytes. *(From Floege J, Amann K. Primary glomerulonephritides. Lancet. 2016;387:2036–2046. Fig. 3.)*

CLINICAL MANIFESTATIONS

In children, MN is most common in the second decade of life, but it can occur at any age, including infancy. The disease usually manifests as nephrotic syndrome and accounts for 2–6% of all cases of childhood nephrotic syndrome. Most patients also have microscopic hematuria and only rarely present with gross hematuria. Approximately 20–30% of children have hypertension at presentation. A subset of patients with MN present with a major venous thrombosis, commonly **renal vein thrombosis**. This complication of nephrotic syndrome (see Chapter 567) is particularly common in patients with MN. Serum C3 and CH_{50} levels are normal, except in secondary forms such as in systemic lupus erythematosus, where levels may be depressed (see Fig. 559.6).

DIAGNOSIS

MN might be suspected on clinical grounds, particularly in the setting of known risk factors for secondary forms of the disease. In the past, the diagnosis could be established only by renal biopsy, but testing for PLA2R antibodies has allowed a noninvasive way to make the diagnosis, to differentiate primary vs secondary MN, and to guide treatment decisions. Common indications for renal biopsy leading to the diagnosis of MN include presentation with nephrotic syndrome in a child >10 years old or unexplained persistent hematuria with significant proteinuria.

PROGNOSIS AND TREATMENT

The clinical course of idiopathic membranous glomerulopathy is variable. Children presenting with asymptomatic, low-grade proteinuria can enter remission spontaneously. Retrospective reports of children 1-15 years after diagnosis treated with a variety of regimens indicate that 20% progress to chronic renal failure, 40% continue with active disease, and 40% achieve complete remission. Poor prognostic factors include male gender, high levels of proteinuria, reduced kidney function, and findings of glomerulosclerosis and tubular damage in the renal biopsy. Although no controlled trials have been performed in children, immunosuppressive therapy with an extended course of prednisone can be effective in promoting complete resolution of symptoms. The addition of chlorambucil or cyclophosphamide provides further benefit to those not responding to steroids alone. Rituximab has shown significant promise in adults and has been proposed by some as the first-line treatment but has yet to be studied in a randomized controlled trial in any age-group. For those unresponsive to immunosuppression, or with mild clinical features, proteinuria can be reduced with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

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559.6 Membranoproliferative Glomerulonephritis

Francisco X. Flores

Membranoproliferative glomerulonephritis (MPGN), also known as **mesangiocapillary glomerulonephritis**, most commonly occurs in older children or young adults. MPGN can be classified into *primary* (idiopathic) and *secondary* forms of glomerular disease. Secondary forms of MPGN are most commonly associated with subacute and chronic infection, including hepatitis B and C, syphilis, endocarditis, and infected shunts, especially ventriculoatrial

shunts (shunt nephritis) (Table 559.2). MPGN can also be one of the glomerular lesions seen in lupus nephritis (see Chapter 560.2).

PATHOLOGY

Primary MPGN is defined by the histologic pattern of glomeruli as seen by light, immunofluorescence, and electron microscopy. Two subtypes have been defined on histologic criteria and are associated with different clinical phenotypes. **Type I MPGN** is most common. Glomeruli have an accentuated lobular pattern from diffuse mesangial expansion, endocapillary proliferation, and an increase in mesangial cells and matrix. The glomerular capillary walls are thickened, often with splitting from interposition of the mesangium. Crescents, if present, indicate a poor prognosis. Immunofluorescence microscopy reveals C3 and lesser amounts of immunoglobulin in the mesangium and along the peripheral capillary walls in a lobular pattern. Electron microscopy confirms numerous deposits in the mesangial and subendothelial regions.

Far less common is **type II MPGN,** also called **dense deposit disease,** which has similar light microscopic findings as type I MPGN. Differentiation from type I disease is by immunofluorescence and electron microscopy. In type II disease, C3 immunofluorescence typically is prominent, without concomitant immunoglobulin. By electron microscopy, the lamina densa in the GBM undergoes a very dense transformation, without evident immune complex–type deposits.

C3 glomerulonephritis (C3GN) is a related but separate diagnostic category. By light and electron microscopy C3GN usually has features indistinguishable from classic MPGN. Immunofluorescence studies distinguish between the two, with C3GN having only C3 deposition and MPGN having both C3 and immunoglobulin fluorescence.

PATHOGENESIS

Although the histology of type I MPGN produced by primary and secondary forms is indistinguishable, it appears that type I disease occurs when circulating immune complexes become trapped in the glomerular subendothelial space, which then causes injury, resulting in the characteristic proliferative response and mesangial expansion. Further evidence confirming this pathway to glomerular injury is the finding of complement activation through the classic pathway in as many as 50% of affected patients.

Type II MPGN appears *not* to be mediated by immune complexes. The pathogenesis of the disease is not known, but the characteristic finding of severely depressed serum complement levels suggests that deranged complement regulation might play a major role in the disease. A typical finding is markedly depressed serum C3 complement levels, with normal levels of other complement components. In many patients with type II MPGN, **C3 nephritic factor** (ant–C3 convertase antibody) is present. This factor activates the alternative complement pathway. In unusual cases, patients with type II MPGN demonstrate an associated systemic disease called **partial lipodystrophy,** where there is diffuse loss of adipose tissue and decreased complement in the presence of C3 nephritic factor. The correlation between the presence of C3 nephritic factor, complement levels, and disease presence or severity is not strong, indicating that the complement abnormalities alone are not sufficient to cause the disease.

Type II MPGN (dense deposit disease) is considered part of the broader spectrum of C3GN. The latter, as defined previously pathologically, appears to be caused by primary dysregulation of the alternative or terminal cascade complement pathways.

CLINICAL MANIFESTATIONS

MPGN is most common in the second decade of life, equally affects males and females, and is more common in White individuals. Systemic features may provide clues to which type of MPGN may be present, but the two histologic types of idiopathic MPGN are indistinguishable in terms of their renal manifestations. Patients present in equal proportions with nephrotic syndrome, acute nephritic syndrome (hematuria, hypertension, and some level of renal dysfunction), or persistent asymptomatic microscopic hematuria and proteinuria. Serum C3 complement levels are low in the majority of cases (see Fig. 559.6).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes all forms of acute and chronic glomerulonephritis, including idiopathic and secondary forms, along with postinfectious glomerulonephritis. Postinfectious glomerulonephritis, far more common than MPGN, usually does not have nephrotic features but typically has hematuria, hypertension, renal dysfunction, and transiently low C3 complement, all features that may be seen with MPGN or C3GN. In contrast to MPGN and C3GN, where C3 levels usually remain persistently low, C3 returns to normal within 8-10 weeks after the onset of postinfectious glomerulonephritis (see Chapter 559.4). The diagnosis of MPGN is made by renal biopsy. Indications for biopsy include nephrotic syndrome in an older child, significant proteinuria with microscopic hematuria, and hypocomplementemia lasting >2 months in a child with acute nephritis. If C3 but no immunoglobulin deposition is found in glomeruli with MPGN, genetic testing and functional assays to define defects of complement cascade regulation should be pursued.

PROGNOSIS AND TREATMENT

It is important to determine whether MPGN is idiopathic or secondary to a systemic disease, particularly lupus or chronic infection, because treatment of the causative disease can result in resolution of the MPGN. Untreated, idiopathic MPGN, regardless of type, has a poor prognosis. By 10 years following onset, 50% of patients with MPGN have progressed to end-stage renal disease. By 20 years following onset, up to 90% have lost renal function. Those with nephrotic syndrome and hypertension at the time of presentation progress to renal failure more rapidly. No definitive therapy exists, but several reports, including a randomized controlled trial, indicate that extended courses of alternate-day prednisone (for years) provide benefit. Some patients treated with steroids enter a complete clinical remission of their disease, but many have ongoing disease activity. Nevertheless, an extended course of prednisone is associated with significant preservation of renal function when compared with patients receiving no such treatment.

The prognosis of C3GN, separate from dense deposit disease (considered a part of C3GN by some) and other forms of classically defined MPGN, is as yet hard to define because reports of the outcome of such patients previously had been grouped in studies of all forms of MPGN (types I and II, and even a poorly characterized type III form not considered earlier). The apparent pathophysiology of C3GN promises that treatments targeting the interruption of complement activation pathways, such as complement factor H replacement or shutting down the terminal complement cascade by blocking C5 activation with eculizumab (anti–C5 antibody), could be beneficial in preventing the progression of renal disease.

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559.7 Rapidly Progressive (Crescentic) Glomerulonephritis

Francisco X. Flores

Rapidly progressive describes the clinical course of several forms of glomerulonephritis (GN) that have the unifying feature of a histopathologic finding of crescents in the majority of glomeruli (Fig. 559.9). The terms *rapidly progressive glomerulonephritis* (RPGN) and *crescentic glomerulonephritis* (CGN) are synonymous. The natural history of most forms of CGN is the rapid loss of the renal function.

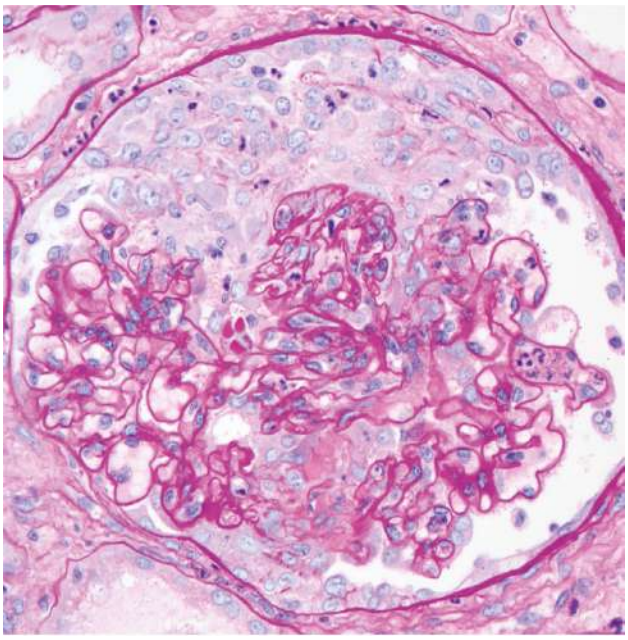

Fig. 559.9 Light micrograph showing a cellular crescent in Bowman's space. The underlying glomerular tuft is delineated by the glomerular basement membranes. (Periodic acid-Schiff stain, x500.) *(From Saha MK, Pendergraft WF, Jennette JC, Falk RJ. Primary glomerular dsease. In Yu AS, Chertow, G, et al, eds. Brenner and Rector's The Kidney, 11th edition. Philadelphia: Elsevier; 2020: Fig. 31.34.)*

CLASSIFICATION

CGN can be a severe manifestation of essentially every defined primary and secondary GN, but particular forms of GN are more likely to present as, or evolve into, RPGN (Table 559.3). If no underlying cause is identified by systemic features, serologic testing, or histologic examination, the disease is classified as idiopathic CGN. The incidence of specific etiologies of CGN in children varies widely; certain common themes are shared in all such reports. Patients with systemic vasculitis appear to be particularly prone to develop CGN. Patients with IgA vasculitis, antineutrophil cytoplasmic antibody (ANCA)-mediated GN (microscopic polyangiitis and granulomatosis with polyangiitis), and systemic lupus erythematosus account for the majority of patients with CGN. Postinfectious GN or endocarditis rarely progresses to CGN, but because it is the most common form of GN in childhood, it accounts for a significant percentage of patients with CGN in most reports. MPGN and idiopathic disease make up most of the remaining cases of CGN. IgA nephropathy, a common GN, only rarely is rapidly progressive. Goodpasture disease often has rapidly progressive GN as a component of the syndrome, but its rarity in childhood results in only a small percentage of children with CGN.

PATHOLOGY AND PATHOGENESIS

The hallmark of CGN is the histopathologic finding of epithelial crescents involving 50% or more glomeruli (see Fig. 559.9). Crescent formation, through proliferation of parietal epithelial cells in Bowman's space, may be the final pathway of any severe inflammatory glomerular injury. Podocytes and renal progenitor cells are involved in the pathogenesis of CGN. Fibrous crescents, in which proliferative cellular crescents are replaced by collagen, are a late finding. The immunofluorescence findings, as well as the pattern of any deposits by electron microscopy, can delineate the underlying glomerulopathy in CGN secondary to lupus, IgA vasculitis nephritis, MPGN, postinfectious GN, IgA nephropathy, or Goodpasture disease. Rare or absent findings by immunofluorescence and electron microscopy typify pauciimmune GN (granulomatosis with polyangiitis and microscopic polyangiitis) and idiopathic crescentic GN.

Table 559.3 Classification of Rapidly Progressive (Crescentic) Glomerulonephritis

PRIMARY
Anti–glomerular basement membrane antibody disease
Goodpasture syndrome (with pulmonary disease)
Immune complex mediated
Pauci-immune (usually antineutrophil cytoplasmic antibody positive)
SECONDARY
Membranoproliferative glomerulonephritis
Immunoglobulin A nephropathy, IgA vasculitis
Poststreptococcal glomerulonephritis
Systemic lupus erythematosus

CLINICAL MANIFESTATIONS

Most children present with acute nephritis (hematuria, various degrees of renal dysfunction, and hypertension) and usually have concomitant proteinuria, often with nephrotic syndrome. Occasional patients present late in the course of disease with oliguric renal failure. Extrarenal manifestations, such as pulmonary involvement, joint symptoms, or skin lesions, can help lead to the diagnosis of the underlying systemic disease causing the CGN.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of CGN is made by obtaining a kidney biopsy. Delineation of the underlying etiology is reached by a combination of additional biopsy findings (described earlier), extrarenal symptoms and signs, and serologic testing, including the evaluation of antinuclear and anti-DS DNA antibodies, serum complement levels, anti-GBM antibodies, and ANCA titers. If the patient has no extrarenal manifestations and a negative serologic evaluation, and if the biopsy has no immune or electron microscopy deposits, the diagnosis is idiopathic, rapidly progressive CGN.

PROGNOSIS AND TREATMENT

The natural course of CGN is far more severe in the setting of other etiologies, including the idiopathic category, and progression to end-stage kidney disease within weeks to months from the onset is common. Having a majority of fibrous crescents on a renal biopsy portends a poor prognosis, because the disease usually has progressed to irreversible damage. Although there are few controlled data, the consensus of most nephrologists is that the combination of high-dose corticosteroids and cyclophosphamide may be effective in preventing progressive renal failure in patients with systemic lupus erythematosus, IgA vasculitis nephritis, granulomatosis with polyangiitis, and IgA nephropathy if given early in the course when acute cellular crescents predominate. Although such therapy can also be effective in the other diseases causing RPGN, renal outcomes in those settings are less favorable. Progression to end-stage kidney disease often occurs despite aggressive immunosuppressive therapy. In combination with immunosuppression, plasmapheresis has been reported to benefit patients with Goodpasture disease. Plasmapheresis may also benefit patients with ANCA-associated CGN, in particular those with the most severe renal dysfunction and pulmonary hemorrhage at presentation. The possible benefits of plasmapheresis in other forms of RPGN are unclear.

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Chapter 560

Multisystem Disease Associated with Hematuria

Prasad Devarajan

Gross or microscopic hematuria may be associated with several multisystem disorders, including chronic systemic infections, systemic lupus erythematosus (SLE), IgA vasculitis nephritis (formerly known as Henoch-Schönlein purpura nephritis), Goodpasture disease, hemolytic uremic syndrome (HUS), nephrotoxicity, and renal cortical necrosis. In most of these conditions, the presenting complaints pertain primarily to the underlying systemic illness, and hematuria often heralds or portends renal involvement (see Chapters 560.1-560.8).

560.1 Chronic Infections

Prasad Devarajan

Glomerulonephritis (GN) with hematuria is a recognized complication of various chronic infections. Examples include bacterial endocarditis caused by viridans group streptococci and other organisms, and ventriculoatrial shunts infected with *Staphylococcus epidermidis*. Other infections, observed less commonly in children than in adults, include those due to HIV, hepatitis B virus (HBV), or hepatitis C virus; syphilis; and renal candidiasis. Parasitic infections associated with glomerular disease include malaria, schistosomiasis, leishmaniasis, filariasis, hydatid disease, trypanosomiasis, and toxoplasmosis. In each condition, the infecting organism has a low virulence, and the host is chronically infected with a microbial antigen. In the presence of high levels of circulating antigen, the host's antibody response leads to the formation of **immune complexes** that are deposited in the kidneys and initiate glomerular inflammation. Foreign antigens can also stimulate an autoimmune response through the production of antibodies that cross react with such antigens incorrectly recognized as glomerular structural components.

The kidney histopathology in GN due to chronic infections can resemble poststreptococcal GN, membranous GN, or membranoproliferative GN. The clinical manifestations are generally those of an acute nephritic syndrome (active urinary sediment with hematuria, proteinuria, and granular and/or red blood cell (RBC) casts, edema, hypertension) or nephrotic syndrome (proteinuria, edema, hypoalbuminemia). *The serum C3 and CH_{50} complement levels are often decreased due to activation of the classic complement pathway.*

In **HIV-associated nephropathy,** direct viral infection of nephrons occurs because renal cells express a variety of lymphocyte chemokine receptors that are essential for and facilitate viral invasion. The kidney expression of HIV infection is quite variable and includes an immune complex injury and a direct cytopathic effect. The classic histopathologic lesion of HIV-associated nephropathy is *focal segmental glomerulosclerosis.* In the era of antiretroviral therapy, the decline in mortality from HIV disease has led to the increased recognition of renal disorders as an important long-term complication in children who survive perinatal HIV infection.

HBV infection is a global public health problem. It is estimated that there are more than 350 million HBV carriers in the world.

Prompt eradication of any infection before severe glomerular injury occurs usually results in resolution of the GN associated with chronic infections. Progression to end-stage kidney disease has been described but is uncommon. Spontaneous resolution of hepatitis B infection is common in children (30–50%) and results in remission of the glomerulopathy. Widespread use of hepatitis B vaccines has decreased the incidence of HBV-related renal diseases. Also, with the new availability of direct-acting antivirals for hepatitis C virus, a sustained virologic response, successful remission, and even regression of glomerular lesions can be achieved if treatment is initiated at an early stage. Similarly, in patients with HIV-associated nephropathy, several clinical studies have demonstrated the overall improvement in kidney function with early initiation of antiretroviral therapy. Particularly in children, modern antiretroviral therapy has improved the outcome and decreased the prevalence of childhood HIV-associated nephropathy.

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560.2 Glomerulonephritis Associated with Systemic Lupus Erythematosus

Prasad Devarajan

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by fever, weight loss, dermatitis, hematologic abnormalities, arthritis, and involvement of the heart, lungs, central nervous system (CNS), and kidneys (see Chapter 199). Although SLE is less frequent in children, kidney involvement (lupus nephritis) is more common and is more severe than that seen in adults. Lupus nephritis is the most important cause of morbidity and mortality in SLE.

PATHOGENESIS AND PATHOLOGY

The hallmark of SLE is the abnormal production of pathogenic autoantibodies to self-antigens such as DNA (anti–double stranded DNA antibody [anti-dsDNA]) and nuclear proteins (antinuclear antibodies [ANA]), driven by immune dysregulation and loss of self-tolerance. The antigen-antibody complexes accumulate in small vessels of many organs, where they incite a local inflammatory response by activating complement pathways and by binding to Fc receptors. Lupus nephritis is a result of the deposition of circulating immune complexes, as well as the direct binding of autoantibodies to glomerular components with resultant complement stimulation.

Kidney biopsy and evaluation of kidney histopathology remain the gold standard for establishing the diagnosis of SLE nephritis and determining specific therapeutic regimens. The World Health Organization (WHO) classification of lupus nephritis has been employed in clinical trials and is based on a combination of features, including light microscopy, immunofluorescence, and electron microscopy. In patients with **WHO class I nephritis** (minimal mesangial lupus nephritis), no histologic abnormalities are detected on light microscopy, but mesangial immune deposits are present on immunofluorescence or electron microscopy. In **WHO class II nephritis** (mesangial proliferative nephritis), light microscopy shows both mesangial hypercellularity and an increased matrix, along with mesangial deposits containing immunoglobulin and complement.

WHO class III nephritis and **WHO class IV nephritis** are interrelated lesions characterized by both mesangial and endocapillary lesions. Class III nephritis is defined by <50% glomeruli with involvement, and class IV has ≥50% glomerular involvement. Immune deposits are present in both the mesangium and subendothelial areas. A **subclassification** scheme helps grade the severity of the proliferative lesion based on whether the glomerular lesions are segmental (<50% glomerular tuft involved) or global (≥50% glomerular tuft involved). The WHO classification scheme also delineates whether there is a predominance of chronic disease versus active disease. Chronic injury results in glomerular sclerosis and is felt to be the consequence of significant proliferative disease seen in classes III and IV. Other signs of active disease include capillary walls that are thickened secondary to subendothelial deposits (creating the characteristic wire-loop lesion), necrosis, and crescent formation. WHO class IV nephritis is associated with poorer outcomes but can be successfully treated with aggressive immunosuppressive therapy.

WHO class V nephritis (membranous lupus nephritis) is less commonly seen as an isolated lesion and resembles idiopathic membranous nephropathy with subepithelial immune deposits. This lesion is often seen in combination with class III or IV proliferative nephritis, and if the membranous lesion is present in >50% glomeruli, both classes are noted in the designation. This classification scheme also identifies cases with combinations of mixed classes III, IV, and V lesions, directing appropriate treatment for such patients.

Another classification scheme proposed by both the International Society of Nephrology and the Renal Pathology Society differs mainly in its subclassification of class IV into diffuse global and diffuse segmental lesions (Table 560.1). Although this classification is widely preferred, it should be noted that most available results of clinical trials are based on the WHO classification.

Transformation of the histologic lesions of lupus nephritis from one class to another is common. This is more likely to occur among inadequately treated patients and usually results in progression to a more severe histologic lesion.

Immunofluorescence microscopy is an essential component of the pathologic evaluation. Lupus nephritis is characterized by the granular deposition of all immunoglobulin isotypes (IgG, IgM, and IgA—also referred to as "full house"), as well as complements (C3, C4, and C1q) in the glomerular mesangium and capillary walls. This pattern of extensive glomerular immune deposition is referred to as full-house immune staining and is diagnostic of lupus nephritis.

CLINICAL MANIFESTATIONS

Most children with SLE are adolescent females (female-to-male ratio of 5:1) and present with extrarenal manifestations. The relative risk of SLE is three- to sevenfold higher in Asian, Black, and Hispanic females compared with White females. Lupus nephritis in Black and Hispanic populations also typically displays an increased severity and worse prognosis. Lupus nephritis affects 80% of pediatric patients with SLE, and although it commonly presents within the first year of diagnosis, may occur at any time during the disease. The clinical findings in patients having milder forms of lupus nephritis (all class I and II, some class III) include hematuria, normal renal function, and proteinuria <1 g/24 hr. Some patients with class III and all patients with class IV nephritis have hematuria and proteinuria, active urinary sediment with cellular casts, hypertension, reduced kidney function, nephrotic syndrome, or acute kidney injury. The urinalysis may be normal on rare occasions in patients with proliferative lupus nephritis. Patients with class V nephritis commonly present with nephrotic syndrome.

Table 560.1 Classification of Lupus Nephritis

CLASS	CLINICAL FEATURES
I. Minimal mesangial LN	No renal findings
II. Mesangial proliferative LN	Mild clinical renal disease; minimally active urinary sediment; mild to moderate proteinuria (never nephrotic) but may have active serology
III. Focal proliferative LN (<50% glomeruli involved) A. Active A/C. Active and chronic C. Chronic	More active sediment changes; often active serology; increased proteinuria (>25% nephrotic); hypertension may be present; some evolve into class IV pattern; active lesions require treatment; chronic do not
IV. Diffuse proliferative LN (>50% glomeruli involved); all may be with segmental or global involvement (S or G) A. Active A/C. Active and chronic C. Chronic	Most severe renal involvement with active sediment, hypertension, heavy proteinuria (frequent nephrotic syndrome), often reduced glomerular filtration rate; serology very active; active lesions require treatment
V. Membranous LN glomerulonephritis	Significant proteinuria (often nephrotic) with less active lupus serology
VI. Advanced sclerosing LN	More than 90% glomerulosclerosis; no treatment prevents renal failure

LN, Lupus nephritis.
From Radhakrishnan J, Appel GB. Glomerular disorders and nephrotic syndromes. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*. 26th ed. Philadelphia: Elsevier; 2020: Table 113.7.

DIAGNOSIS

The diagnosis of SLE is confirmed by the detection of circulating ANA and by demonstrating antibodies that react with native anti-dsDNA. In most patients with active disease, C3 and C4 levels are depressed. In view of the lack of a clear correlation between the clinical manifestations and the severity of the kidney involvement, kidney biopsy should be performed in all patients with SLE who display even minor urinary abnormalities or other clinical evidence for renal disease. Histopathologic findings are used to determine the classification, severity, prognosis, and selection of specific immunosuppressive therapies.

TREATMENT

Current therapies are largely based on the histology, clinical severity, and lessons learned from clinical trials of adults with lupus nephritis. Immunosuppression remains the cornerstone of therapy. The goal of immunosuppressive therapy in lupus nephritis is to produce both a clinical remission, defined as normalization of renal function and proteinuria, and a serologic remission, defined as normalization of anti-DNA antibody, C3, and C4 levels. Therapy is initiated in all patients with prednisone at a dose of 1-2 mg/kg/day in divided doses, followed by a slow steroid taper over 4-6 months beginning 4-6 weeks after achieving a serologic remission.

For patients with more severe forms of nephritis (WHO classes III and IV), more aggressive immunosuppressive regimens are required because corticosteroid therapy alone is insufficient to induce a remission. In general, such regimens are separated into two phases, namely, induction and maintenance. The most commonly employed induction therapy has been six consecutive monthly intravenous infusions of cyclophosphamide at a dose of 500-1,000 mg/m^2. Pulse intravenous methylprednisolone (1,000 mg/m^2) is also used in addition to oral corticosteroids. Maintenance therapy previously consisted of additional cyclophosphamide infusions every 3 months for 18 months, which reduced the risk of progressive renal dysfunction. Serious side effects of cyclophosphamide have included infections, hair loss, hemorrhagic cystitis, and gonadal failure.

As an alternative induction therapy, in adult and pediatric clinical trials, mycophenolate mofetil was as efficacious as, or even superior to, cyclophosphamide, and is increasingly considered for use in children at a dosage of 600 mg/m^2 per dose twice daily. Maintenance therapy using mycophenolate mofetil or azathioprine is also as efficacious as intravenous cyclophosphamide and results in less serious side effects. Mycophenolate mofetil is particularly more efficacious than cyclophosphamide in Black patients. Major side effects of mycophenolate mofetil have included diarrhea, leukopenia, and teratogenicity. Azathioprine, at a single daily dose of 1.5-2.0 mg/kg, may be used as a steroid-sparing agent in patients with WHO class I or II lupus nephritis.

Rituximab, a chimeric monoclonal antibody specific for human CD20, is an alternative that has been shown to induce a remission in adults and children with proliferative lupus nephritis refractory to steroids and other immunosuppressants. Rituximab is used in cases where resistance to conventional treatment is demonstrated. Plasmapheresis is ineffective in lupus nephritis unless there is accompanying thrombotic thrombocytopenic purpura (TTP) or antineutrophilic cytoplasmic antibody (ANCA)-associated disease. Other therapies include belimumab, a fully humanized monoclonal antibody against a type II transmembrane protein that functions in the normal survival and differentiation of B cells; it has been approved by the FDA for use

in SLE. Its role in lupus nephritis, either in combination with current therapies or to replace them, requires further study.

The optimal treatment for class V lupus nephritis remains unclear. On the one hand, the low risk of progression to end-stage kidney disease when compared with proliferative forms of lupus nephritis has encouraged a less aggressive approach. On the other hand, patients with uncontrolled nephrotic syndrome due to class V lupus nephritis are at a high risk of morbidity and may require more aggressive immunosuppression.

Hydroxychloroquine is prescribed for most patients with SLE for extrarenal manifestations but is thought to have a beneficial effect in maintaining the remission in lupus nephritis. It is a rational choice given its low side effect profile. Use of antihypertensive drugs to aggressively treat hypertension, as well as the specific use of drugs that block the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers) to reduce proteinuria, are also important adjuvant therapies that appear to decrease the long-term progression of renal disease.

PROGNOSIS

Overall, kidney survival (defined as chronic kidney disease without progression to end-stage kidney disease therapy) is seen in 80% of patients 10 years after the diagnosis of SLE nephritis. Patients with diffuse proliferative WHO class IV lupus nephritis, poor kidney function at presentation, or persistent nephrotic-range proteinuria exhibit the highest risk for progression to end-stage kidney disease. Concerns regarding the side effects of chronic immunosuppressive therapy and the risk of recurrent disease are lifelong. Close monitoring for the relapse of disease is critical to ensure maximally successful renal outcomes. Special care must be taken to minimize the risks of infection, osteoporosis, obesity, poor growth, hypertension, and diabetes mellitus associated with chronic corticosteroid therapy. Patients require counseling regarding the risk of malignancy or infertility, which may be increased in those receiving a cumulative dose of >20 g of cyclophosphamide or other immunosuppressant therapies.

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560.3 IgA Vasculitis Nephritis

Prasad Devarajan

IgA vasculitis (formerly known as Henoch-Schönlein purpura) is an idiopathic systemic immune complex–mediated vasculitis associated with IgA deposition within small-vessel walls. It is the most common small-vessel vasculitis in children, with a peak incidence in early childhood (4-6 years of age). Ninety percent of cases occur in children, with about half the cases preceded by an upper respiratory infection. It is characterized by a purpuric rash and commonly accompanied by arthritis and abdominal pain (see Chapter 210.1). Approximately 50% of patients with IgA vasculitis develop kidney manifestations, which vary from asymptomatic microscopic hematuria to severe, progressive GN. IgA vasculitis nephritis shares a similar pathogenesis and nearly identical kidney histology with IgA nephropathy. Although the two are considered as distinct entities, many consider IgA vasculitis nephritis and IgA nephropathy as part of the same clinical spectrum and IgA nephropathy as one of the sequelae of IgA vasculitis nephritis.

PATHOGENESIS AND PATHOLOGY

The pathogenesis of IgA vasculitis nephritis appears to be mediated by the deposition of **polymeric IgA** in glomeruli. This is analogous to the same type of IgA deposits seen in systemic small vessels in IgA vasculitis, primarily those of the skin and intestine. Studies have identified defective glycosylation of the hinge region of IgA1 in patients with both IgA vasculitis nephritis and IgA nephropathy. Recognition of the exposed hinge region of IgA1 by naturally occurring autoantibodies leads to formation of immune complexes that are deposited in the glomerular mesangium. Any mucosal infection or food antigen may trigger the increased production of pathogenic IgA1. IgA immune complexes are deposited throughout the body and activate pathways leading to necrotizing vasculitis. A skin biopsy characteristically shows leukocytoclastic vasculitis with IgA, C3, and fibrin deposition. The glomerular findings can be indistinguishable from those of IgA nephropathy. Pathognomonic IgA deposits are detected by immunofluorescence as the dominant immunoglobulin in the glomerular mesangium. Histologically, a broad spectrum of glomerular lesions that can range from mild mesangial and endocapillary proliferation to necrotic and crescentic changes from extracapillary proliferation can be seen.

CLINICAL AND LABORATORY MANIFESTATIONS

The classic tetrad of IgA vasculitis nephritis includes a palpable purpura, arthritis or arthralgia, abdominal pain, and evidence for kidney disease. *These may develop over a period of days to weeks and may vary in their order of presentation.* Notably, not all of the tetrad are present in all patients. The nephritis associated with IgA vasculitis usually *follows* the onset of the rash, often presenting weeks or even months after the initial nonkidney manifestations have resolved. Nephritis can be manifest at the initial presentation but only rarely before onset of the rash. Some degree of kidney involvement occurs in approximately 50% of IgA vasculitis cases, more commonly in older children (age >8 years confers a threefold greater risk for kidney involvement). Most patients (80%) initially display only mild renal involvement, principally isolated microscopic hematuria without significant proteinuria. About 20% of patients can present with a more severe kidney involvement, including a combined acute nephritic and nephrotic picture (hematuria, hypertension, renal insufficiency, significant proteinuria, and nephrotic syndrome). Older children (and adults) have a greater risk for more severe involvement. Initial mild kidney involvement can also occasionally progress to more severe nephritis despite resolution of all other features of IgA vasculitis. The severity of the systemic manifestations is not correlated with the severity of the nephritis. *Most patients who develop nephritis have urinary abnormalities by 1 month, and nearly all have abnormalities by 3-6 months after the onset of IgA vasculitis.* Therefore a urinalysis (and blood pressure checks) should be performed weekly in patients with IgA vasculitis during the period of active clinical disease (usually during the first 4 weeks). Thereafter, a urinalysis (and blood pressure checks) should be performed once a month for up to 6 months. If all urinalyses and blood pressures are normal during this follow-up interval, nephritis is unlikely to develop. If proteinuria, kidney insufficiency, or hypertension develops along with hematuria, consultation with a pediatric nephrologist is indicated. Indications for a kidney biopsy in children with IgA vasculitis nephritis include significant proteinuria (urine protein >1 g/day or urine protein/creatinine ratio >1.0), significant hypertension, or elevated serum creatinine.

Mimics of IgA vasculitis include endocarditis (skin, renal) and granulomatosis with polyangiitis (skin, renal).

PROGNOSIS AND TREATMENT

The prognosis of IgA vasculitis nephritis for most patients is excellent. Spontaneous and complete resolution of the nephritis typically occurs in many patients with mild initial manifestations (isolated hematuria with insignificant proteinuria). However, such patients uncommonly can progress to severe kidney involvement, including development of chronic kidney disease. Patients with acute nephritic or nephrotic syndrome at presentation have a guarded kidney prognosis, particularly if they are found to have concomitant necrosis or substantial crescentic changes on kidney biopsy. Untreated, the risk of developing chronic kidney disease, including end-stage kidney disease, is 2–5% in all patients with IgA vasculitis, but almost 50% in those with the most severe early kidney clinical and histologic features.

No controlled studies have demonstrated any efficacy of short courses (weeks) of oral corticosteroids administered promptly after the onset of IgA vasculitis in either preventing the development of nephritis or decreasing the severity of subsequent kidney involvement. Tonsillectomy has been proposed as an intervention for IgA vasculitis nephritis, but it also does not appear to have any measurable effect on

the renal outcome. Mild IgA vasculitis nephritis does not require treatment because it usually resolves spontaneously.

The efficacy of treatment for moderate or severe IgA vasculitis nephritis, which is far more likely to progress to chronic kidney disease, is more difficult to assess. Several uncontrolled studies have reported a significant benefit from aggressive immunosuppression (high-dose and extended courses of corticosteroids with azathioprine, mycophenolate mofetil, or cyclophosphamide) in patients with poor prognostic features on kidney biopsy; such patients are at high risk of progressing to chronic kidney disease. Reports of the treatment of high-risk patients with either plasmapheresis or rituximab have also indicated a potential benefit. Balancing the absence of controlled data with the severe side effects of aggressive therapies in patients with poor renal prognostic factors is difficult. Aggressive therapy with careful monitoring may be reasonable in those with the most severe IgA vasculitis nephritis (>50% crescents on biopsy). One common approach in children with severe clinical kidney involvement (nephrotic range proteinuria, elevated serum creatinine, hypertension) is the use of oral prednisone (1 mg/kg/day for 3 months), along with angiotensin-converting enzyme inhibitors, followed by azathioprine or mycophenolate mofetil if severe clinical involvement persists. For children with severe histologic manifestations (>50% glomerular crescents), treatment with intravenous methylprednisolone pulses for 3 days, followed by a combination of oral prednisone (for 3 months) and azathioprine or mycophenolate mofetil (extended course) may be considered. For children with the most severe histology (>75% glomerular crescents) and progressive kidney disease, intravenous steroids plus plasmapheresis may be considered. If progression to end-stage kidney disease occurs, renal transplantation is the treatment of choice. Deposition of IgA in the transplanted kidney is common, but most cases are subclinical, and the overall graft survival is similar to that for other renal transplant recipients.

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560.4 Goodpasture Disease

Prasad Devarajan

Goodpasture disease is an autoimmune disease characterized by pulmonary hemorrhage, **rapidly progressive glomerulonephritis**, and elevated **anti–glomerular basement membrane (anti-GBM) antibody** titers. The disease results from an attack on these organs by antibodies directed against certain epitopes of type IV collagen, located within the alveolar basement membrane in the lung and glomerular basement membrane (GBM) in the kidney. An acquired conformational change in the noncollagenous 1 domain of the alpha 3-chain of type IV collagen leads to the production of pathologic autoantibodies. The high affinity of these antibodies to the GBM results in the characteristic rapidly progressive kidney disease. Infusion of human anti-GBM antibodies into animals reproduces the rapidly aggressive glomerulonephritis, confirming the high pathogenicity of these antibodies.

PATHOLOGY

Kidney biopsy shows proliferative crescentic glomerulonephritis in most patients. Immunofluorescence microscopy demonstrates the pathognomonic continuous linear deposition of immunoglobulin G along the GBM (Fig. 560.1).

CLINICAL MANIFESTATIONS

Goodpasture disease is rare in childhood. Patients usually present with hemoptysis from pulmonary hemorrhage that can be life-threatening. Concomitant renal manifestations include acute glomerulonephritis with hematuria, nephritic urinary sediment with cellular casts, proteinuria, and hypertension, which usually follow a rapidly progressive course. Kidney failure commonly develops within days to weeks of the clinical presentation. Although fever may be present, other systemic complaints such as malaise or arthralgia are usually absent; their presence should raise suspicion for a systemic vasculitis. *Less commonly, patients can have anti-GBM nephritis manifesting as isolated, rapidly progressive glomerulonephritis without pulmonary hemorrhage.* In essentially all cases, anti-GBM antibody is present in the serum and/or the kidney, and the serum complement C3 level is normal. **Antineutrophilic cytoplasmic antibody (ANCA)** levels can be found to be elevated in 10–40% of patients, along with the anti-GBM antibody; such patients doubly positive for these autoantibodies have more severe disease at presentation. In general, anti-GBM antibody titers are correlated with the severity of the renal involvement. However, a kidney biopsy should be performed (unless contraindicated) because the accuracy of anti-GBM serology is variable, and renal biopsy provides additional histologic information that can guide therapy.

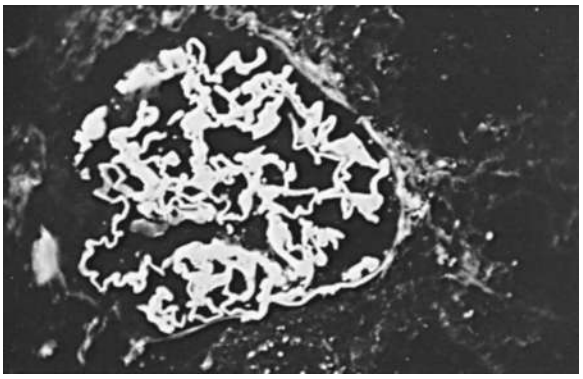

Fig. 560.1 Immunofluorescence micrograph demonstrating the continuous linear staining of immunoglobulin G along the glomerular basement membrane in Goodpasture disease (×250).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is made by a combination of the clinical presentation of pulmonary hemorrhage with acute glomerulonephritis, the presence of serum antibodies directed against GBM (anti–type IV collagen in GBM), and characteristic renal biopsy findings. Other diseases that can cause a **pulmonary-renal syndrome** need to be considered and include SLE, IgA vasculitis, nephrotic syndrome–associated pulmonary embolism, and ANCA-associated vasculitis (such as granulomatosis with polyangiitis and microscopic polyangiitis). These diseases are ruled out by the absence of other characteristic clinical features, kidney biopsy findings, and negative serologic studies for antibodies against nuclear (ANA), DNA (anti-dsDNA), and neutrophil cytoplasmic components (ANCA antibody).

PROGNOSIS AND TREATMENT

Untreated, the prognosis of Goodpasture disease is poor. Treatment must be initiated emergently as soon as the diagnosis is suspected. The prompt institution of plasmapheresis, high-dose intravenous methylprednisolone, and cyclophosphamide often induces remission and improves survival times. Initial therapy with plasmapheresis removes circulating anti-GBM antibodies, and initial immunosuppression with steroids and cyclophosphamide inhibits ongoing antibody production. Rituximab may be used as a substitute in cases where cyclophosphamide toxicity is encountered. Initial treatment is guided by the clinical response and serial anti-GBM antibody titers. Retrospective cohort studies suggest that when this combination of treatments is started early, most patients will have a good kidney outcome. However, an initial presentation with oligoanuria, a high proportion of glomerular crescents, or kidney failure requiring dialysis predicts worse kidney and patient survival rates. After the induction of remission, maintenance therapy with lower doses of prednisone and azathioprine (or mycophenolate mofetil) is continued for 6-9 months. However, patients who survive the acute pulmonary hemorrhage and rapidly progressive glomerulonephritis can still progress to end-stage kidney disease despite ongoing immunosuppressive therapy. For patients who

progress, kidney transplantation is the treatment of choice. Relapse and recurrent disease after kidney transplantation are both uncommon.

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560.5 Hemolytic-Uremic Syndrome

Prasad Devarajan

Hemolytic-uremic syndrome (HUS) is a common cause of community-acquired acute kidney injury in young children. It is the most common form of **thrombotic microangiopathy (TMA)** in children (Fig. 560.2). Like all TMAs, HUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and kidney insufficiency. HUS has clinical features in common with thrombotic thrombocytopenic purpura (TTP) (see Chapter 533.5). The etiology and pathophysiology of the more common forms of HUS clearly delineate typical childhood HUS as separate from idiopathic TTP.

ETIOLOGY

The various etiologies of HUS and other related thrombotic microangiopathies allow classification into infection-induced, genetic, drug-induced, and HUS associated with systemic diseases characterized by microvascular injury (Table 560.2; see Fig. 560.2). The most common form of HUS is caused by **Shiga toxin–producing *Escherichia coli* (STEC)**, which causes prodromal acute enteritis and is commonly termed STEC-HUS or *diarrhea-associated HUS*. In the subcontinent of Asia and in southern Africa, the toxin of *Shigella dysenteriae* type 1 is causative, whereas in Western countries, verotoxin or STEC is the usual cause. STEC-HUS accounts for about 90% of all HUS cases in childhood.

Several serotypes of *E. coli* can produce the toxin. O157:H7 is most common in Europe and the Americas; other serotypes include O26, O111, O121, O145, O91, O103, O104, and O80. The reservoir of STEC is the intestinal tract of domestic animals, usually cows. Disease commonly is transmitted by undercooked meat or unpasteurized (raw) milk and apple cider. Local outbreaks have followed the ingestion of undercooked, contaminated hamburger or other foods cross-contaminated on unwashed cutting boards at fast food restaurants; contaminated municipal water supplies; petting farms; and swimming in contaminated ponds, lakes, or pools. With broad food distribution, wider epidemics have been traced to lettuce, raw spinach, and bean sprouts contaminated with STEC. Less often, STEC has been spread by person-to-person contact within families or childcare centers.

A rare but distinct entity of infection-triggered HUS is related to neuraminidase-producing *Streptococcus pneumoniae* (Sp-HUS). Sp-HUS, typically severe, develops during acute infection with this organism, typically manifesting as pneumonia with empyema. Compared with the prevaccine era, Sp-HUS incidence seems to be decreasing after the introduction of 7-serotype valent and 13-serotype valent pneumococcal vaccines. However, severe Sp-HUS cases continue to occur secondary to vaccine failure and emergence of nonvaccine/replacement serotypes. A TMA, similar to HUS or TTP, also can occur in patients with untreated HIV infection and influenza infection.

Genetic forms of HUS (atypical, nondiarrheal) compose the second major category of the disease (see Table 560.2 and Fig. 560.2). Inherited deficiencies of either von Willebrand factor–cleaving protease (ADAMTS13) or complement factor H, I, or B can cause HUS. A specific genetic defect has not been identified in approximately 50% of familial cases transmitted in classic Mendelian autosomal dominant or

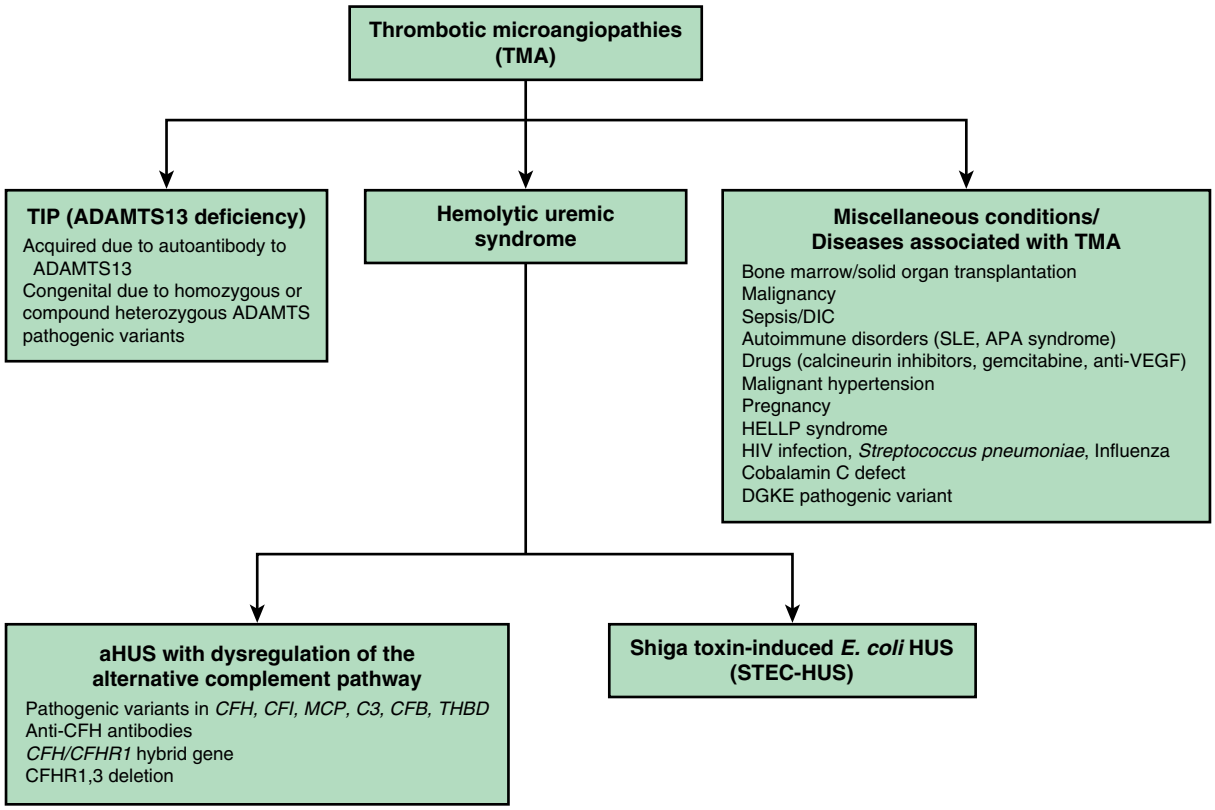

Fig. 560.2 Classification algorithm for the thrombotic microangiopathies based on etiology. ADAMTS13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; APA, antiphospholipid antibody syndrome; CFB, complement Factor B; CFH, complement Factor H; CFI, complement Factor I; DGKE, diacylglycerol kinase ε; DIC, disseminated intravascular coagulation; HELLP syndrome, hemolysis, elevated liver enzymes and low platelet count syndrome; MCP, membrane cofactor protein (CD46); SLE, systemic lupus erythematosus; THBD, thrombomodulin gene; VEGF, vascular endothelial growth factor. *(From Dixon BP, Gruppo RA. Atypical hemolytic uremic syndrome. Pediatr Clin N Am. 2018;65:509–525. Fig. 2.)*

Table 560.2 Current Classification of Hemolytic Uremic Syndromes and Thrombotic Microangiopathies

DIARRHEA-ASSOCIATED HUS
STEC (*Escherichia coli* O157:H7)
STEC (*E .coli* 0121 and 0104:H4)
Non-STEC (*Shigella dysenteriae* type 1)
HUS SECONDARY TO SYSTEMIC INFECTIONS
Neuraminidase (*Streptococcus pneumoniae*)
HIV
Influenza
Human herpes virus 6
Parvovirus B19
Malaria
ATYPICAL HUS DUE TO COMPLEMENT DYSREGULATION
Factor H deficiency (pathogenic variants, autoantibodies)
Factor I deficiency (pathogenic variants)
Factor B (gain-of-function pathogenic variants)
Membrane cofactor (MCP) deficiency (pathogenic variants)
C3 deficiency (pathogenic variants, autoantibodies)
Thrombomodulin deficiency (pathogenic variants)
Anti–complement factor H antibody
Unknown
THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)
Inherited ADAMTS13 deficiency (pathogenic variants)
Acquired ADAMTS13 deficiency (antibody-mediated)
Pregnancy-associated
Vitamin B_{12} deficiency
DRUG INDUCED
Cyclosporine
Tacrolimus
Bleomycin
Mithramycin
Cisplatin
Quinine
Cocaine
Anti–vascular endothelial growth factor (anti-VEGF) drugs
SYSTEMIC DISEASE ASSOCIATED
Systemic lupus erythematosus
Coexisting nephropathies
Malignant hypertension
Malignancies
Cobalamin C defect
Diacylglycerol kinase epsilon pathogenic variant
TRANSPLANT ASSOCIATED
Stem cell transplant
Bone marrow transplant
Renal
Heart
Intestinal

recessive patterns. Some of these may be due to cobalamin C pathogenic variants. A major feature characteristic of genetic forms of HUS is the *absence* of a preceding diarrheal prodrome, although the presence of a diarrheal prodrome does not rule out atypical HUS. Genetic forms of HUS can be indolent and unremitting once they become manifest, or they can have a relapsing pattern precipitated by an infectious illness. The latter feature likely explains the association of many infectious agents with HUS, particularly in reports published before the recognition of the unique pathophysiology of STEC and neuraminidase-producing pneumococci in causing HUS.

HUS can be superimposed on any disease associated with microvascular injury, including malignant hypertension, SLE, and antiphospholipid syndrome. It can also occur after bone marrow or solid organ transplantation and may be triggered by the use of the calcineurin inhibitors cyclosporine and tacrolimus in that setting. Several other medications also can induce HUS (see Table 560.2 and Fig. 560.2).

PATHOLOGY

Kidney biopsies are only rarely performed in HUS because the diagnosis is usually established by clinical criteria, and the risks of biopsy are significant during the active phase of the disease. Early glomerular changes include thickening of the capillary walls caused by swelling of endothelial cells and accumulation of fibrillar material between endothelial cells and the underlying basement membrane, causing narrowing of the capillary lumens. Platelet-fibrin thrombi are often seen in glomerular capillaries. Thrombi are also seen in afferent arterioles and small arteries with fibrinoid necrosis of the arterial wall, leading to kidney cortical necrosis from vascular occlusion. Late findings include glomerular sclerosis and obsolescence secondary to either severe direct glomerular involvement or glomerular ischemia from arteriolar involvement.

PATHOGENESIS

Microvascular injury with endothelial cell damage is characteristic of all forms of TMA, including HUS. In the diarrhea-associated form of HUS, enteropathic organisms produce either Shiga toxin or the highly homologous Shiga-like verotoxin. These toxins are easily absorbed from the colonic mucosa into the systemic circulation, bind to endothelial cells in the glomerulus and elsewhere, and directly cause endothelial cell damage. Shiga toxin can also directly activate platelets to promote their aggregation. Mechanical injury to RBCs passing through the thrombotic microvasculature results in a severe nonimmune anemia with a negative direct Coombs test. In pneumococcal-associated HUS, neuraminidase cleaves sialic acid on membranes of endothelial cells, red cells, and platelets to expose the underlying cryptic Thomsen-Friedenreich (T) antigen. Endogenous IgM antibodies recognize and react with the T antigen to trigger hemolysis and anemia with a positive direct Coombs test.

The *familial* recessive and dominant forms of HUS, including the inherited deficiencies of ADAMTS13 and regulators of the complement cascade, probably predispose patients to developing HUS but do not cause the disease per se because these patients might not develop HUS until later childhood or even adulthood. In such cases, HUS is often triggered by an inciting event such as an infectious disease. The absence of ADAMTS13 impairs cleavage of von Willebrand factor multimers, which enhances platelet aggregation. Factor H plays a central role in complement regulation, primarily arresting the amplification and propagation of complement activation. It is possible that mild endothelial injury that would normally resolve instead evolves to an aggressive microangiopathy because of the inherited deficiencies of these factors.

In each form of HUS, capillary and arteriolar endothelial injury in the kidney leads to localized thrombosis, particularly in glomeruli, causing a direct decrease in glomerular filtration. Progressive platelet aggregation in the areas of microvascular injury results in consumptive thrombocytopenia. Microangiopathic hemolytic anemia results from mechanical damage to RBCs as they pass through the damaged and thrombotic microvasculature.

CLINICAL MANIFESTATIONS

Typical HUS (diarrhea form) is most common in preschool- and school-age children, but it can occur in adolescents and adults. In HUS caused by toxigenic *E. coli,* the onset of HUS occurs 5-7 days after the onset of gastroenteritis with fever, vomiting, abdominal pain, and diarrhea. The prodromal intestinal symptoms may be severe and require hospitalization, but they can also be relatively mild and considered trivial. Not all infected patients will develop HUS. The diarrhea is often bloody but not necessarily so. After the prodromal illness, the sudden onset of pallor, weakness, and lethargy heralds the onset of HUS, and it reflects the development of microangiopathic hemolytic anemia. Oliguria can be present in early stages but may be masked by ongoing diarrhea because the prodromal enteritis often overlaps the onset of HUS, particularly with ingestion of large doses of toxin. Thus patients with HUS can present with either significant dehydration or volume overload, depending on whether the enteritis or kidney insufficiency from HUS predominates and the amount of fluid that has been administered.

Patients with pneumococci-associated HUS usually are quite ill with pneumonia, empyema, and bacteremia when they develop HUS. The onset can be insidious in patients with the genetic forms of HUS, with HUS triggered by a variety of illnesses, including mild, nonspecific gastroenteritis or respiratory tract infections.

HUS can be relatively mild or can progress to a severe and fatal multisystem disease. Leukocytosis, severe prodromal enteritis, hyponatremia, and antibiotic use portend a severe course, but no presenting features reliably predict the severity of HUS in any given patient. Patients with HUS who appear mildly affected at presentation can rapidly develop severe, multisystem, life-threatening complications. Kidney insufficiency can be mild but also can rapidly evolve into severe oliguric or anuric kidney failure. The combination of rapidly developing kidney failure and severe hemolysis can result in life-threatening hyperkalemia. Severe acute kidney injury requiring dialysis develops in about 50% of patients with STEC-HUS. The duration of the dialysis requirement is usually about 2 weeks. Volume overload, hypertension, and severe anemia can all develop soon after the onset of HUS and together can precipitate heart failure. Direct **cardiac involvement** is rare, but pericarditis, myocardial dysfunction, or arrhythmias can occur without predisposing features of hypertension, volume overload, or electrolyte abnormalities.

The majority of patients with HUS have some **CNS involvement**. Most have mild manifestations, with significant irritability, lethargy, or nonspecific encephalopathic features. Severe CNS involvement occurs in ≤20% of cases. Seizures and significant encephalopathy are the most common manifestations in those with severe CNS involvement, resulting from focal ischemia secondary to microvascular CNS thrombosis. Small infarctions in the basal ganglion and cerebral cortex have also been reported, but large strokes and intracranial hemorrhage are rare. Hypertension may produce an encephalopathy and seizures. Intestinal complications can be protean and include severe inflammatory colitis, ischemic enteritis, bowel perforation, intussusception, and pancreatitis. Patients can develop petechiae, but significant or severe bleeding is rare despite very low platelet counts.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is made by the combination of microangiopathic hemolytic anemia with schistocytes, thrombocytopenia, and some degree of kidney involvement. The anemia can be mild at presentation, but it rapidly progresses. Thrombocytopenia is an invariable finding in the acute phase, with platelet counts usually 20,000-100,000/mm^3. Partial thromboplastin and prothrombin times are usually normal. The Coombs test is negative, except in pneumococci-induced HUS, where the Coombs test is usually positive. Leukocytosis is often present and significant. Urinalysis typically shows microscopic hematuria and low-grade proteinuria. The kidney insufficiency can vary from mild elevations in serum BUN and creatinine to acute, anuric kidney failure.

The etiology of HUS is often clear with the presence of a diarrheal prodrome or pneumococcal infection. The presence or absence of toxigenic organisms on stool culture has little role in making the diagnosis of diarrhea-associated STEC-HUS. Only a minority (~10%) of patients infected with those organisms develops HUS, and the organisms that cause HUS may be rapidly cleared. Therefore the stool culture may be negative in patients who have diarrhea-associated HUS. If no history of diarrheal prodrome or pneumococcal infection is obtained, then evaluation for genetic forms of HUS should be considered because those patients are at risk for recurrence, have a severe prognosis, and can benefit from specific therapy. Other causes of acute kidney injury associated with a microangiopathic hemolytic anemia and thrombocytopenia should be considered and excluded, such as SLE, malignant hypertension, and bilateral renal vein thrombosis. A kidney biopsy is rarely indicated to diagnose HUS.

PROGNOSIS AND TREATMENT

With early recognition and intensive supportive care, the mortality rate for diarrhea-associated HUS is <5%. Up to half of patients may require dialysis support during the acute phase of the disease. Recovery of platelet counts usually occurs first, followed by kidney recovery about 5 days later, and finally by resolution of anemia. Most recover kidney function completely, but of surviving patients, 5% remain dependent on dialysis, and up to 30% are left with some degree of chronic kidney disease. The prognosis for HUS not associated with diarrhea is more severe. Pneumococci-associated HUS causes increased patient morbidity (>80% require dialysis), with the mortality rate reported as 20%. The familial, genetic forms of HUS can be insidiously progressive or relapsing diseases and have a poor prognosis. Identification of specific factor deficiencies in some of these genetic forms provides an opportunity for directed therapy to improve the outcome.

The primary approach that has substantially improved an acute outcome in HUS is early recognition of the disease, monitoring for potential complications, and meticulous supportive care. Supportive care includes careful management of fluid and electrolytes, including prompt correction of a volume deficit, control of hypertension, and early institution of dialysis if the patient becomes significantly oliguric or anuric, particularly with hyperkalemia. Early intravenous volume expansion before the onset of oliguria or anuria may be nephroprotective in diarrhea-associated HUS. Red cell transfusions are usually required because hemolysis can be brisk and recurrent until the active phase of the disease has resolved. In pneumococci-associated HUS, it is critical that any administered red cells be washed before transfusion to remove residual plasma, because endogenous IgM directed against the revealed T antigen can play a role in accelerating the pathogenesis of the disease. Platelets should generally not be administered, regardless of the platelet count, to patients with HUS because they are rapidly consumed by the active coagulation and theoretically can worsen the clinical course. Despite low platelet counts, serious bleeding is very rare in patients with HUS.

There is no evidence that any therapy directed at arresting the disease process of the most common, diarrhea-associated STEC-HUS provides benefit, and some can cause harm. Attempts have been made using anticoagulants, antiplatelet agents, fibrinolytic therapy, plasma therapy, immune globulin, and antibiotics. Anticoagulation, antiplatelet, and fibrinolytic therapies are specifically contraindicated because they increase the risk of serious hemorrhage. Antibiotic therapy to clear enteric toxigenic organisms (STEC) can result in increased toxin release, potentially exacerbating the disease; therefore it is not recommended. However, prompt treatment of causative pneumococcal infection is important. The European experience with *E. coli* O104:H4 in adults who were treated with azithromycin demonstrated more rapid elimination of the organism. Furthermore, in vitro evidence suggests that meropenem, rifaximin, and azithromycin downregulate the release and expression of Shiga toxin. Nonetheless, *in children with E. coli O157:H7–associated HUS, antibiotics are still considered contraindicated.*

Plasma infusion or plasmapheresis has been proposed for patients suffering severe manifestations of HUS with serious CNS involvement. There are no controlled data demonstrating the effectiveness of this approach, and it is specifically contraindicated in those with pneumococcal-associated HUS because it could exacerbate the disease. The use of plasma therapy in STEC-HUS was one of many treatment strategies during one of the largest reported outbreaks of STEC-HUS. This outbreak was caused by an uncommon serotype (O104:H4) that had unique virulence factors. Thought initially to cause more severe disease, it differed epidemiologically from other STEC-HUS serotypes by affecting primarily healthy adults, rather than the usual pattern of affecting children and the elderly. Treatment in this epidemic included plasma exchange in most of the adult patients, as well as the use of eculizumab.

Eculizumab is an anti-C5 antibody that inhibits complement activation, a pathway that contributes to active disease in some forms of atypical familial HUS; this pathway may also contribute to the process in STEC-HUS. Eculizumab is approved by the FDA for the treatment of *atypical HUS*. Because of the risk of meningococcal disease in patients with defects in terminal complement components, it is recommended to give the meningococcal vaccine before giving eculizumab (if the patient has not been primarily immunized). Although initial reports suggested that eculizumab provided benefit in patients with

diarrhea-associated HUS, subsequent systematic analysis showed no benefit from either plasma exchange or eculizumab.

Plasma therapy can be of substantial benefit to patients with identified deficits of ADAMTS13 or factor H. It may also be considered in patients with other genetic forms of HUS, such as the undefined familial (recessive or dominant) form or sporadic but recurrent HUS. In contrast to its use in STEC-HUS, eculizumab shows great promise in the treatment of atypical HUS, including HUS occurring following renal transplantation. Whether it should be combined with plasma therapy or used as a primary treatment of atypical HUS is still undetermined.

Most patients with diarrhea-associated HUS recover completely, with little risk of long-term sequelae. Patients with hypertension, any level of kidney insufficiency, or residual urinary abnormalities persisting a year after an episode of diarrhea-positive HUS (particularly significant proteinuria) require careful follow-up. Patients who have recovered completely with no residual urinary abnormalities after 1 year are less likely but may still manifest long-term sequelae. In a multicenter pooled analysis of 3,476 children with hemolytic uremic syndrome followed up for a mean of 4.4 years, the combined average death and end-stage kidney disease rate was 12%, and the combined average kidney sequelae rate (chronic kidney disease, proteinuria, hypertension) was 25%. Because of reports of late sequelae in such patients, annual examinations with a primary physician are still warranted.

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560.6 Toxic Nephropathy

Prasad Devarajan

Aberrant renal function often results from purposeful or accidental exposure to any number of diagnostic, biologic, or therapeutic agents that are potential or actual nephrotoxins. Among diagnostic agents, **contrast-induced nephropathy** is a common and generally reversible form of **acute kidney injury** that results from administration of radiocontrast media in predisposed individuals. Iodinated radiocontrast agents are generally well tolerated by most patients without significant adverse consequences. In volume-depleted patients or patients with underlying chronic kidney disease, their use poses a risk for the development of acute kidney injury with significant attendant morbidity and mortality. Contrast agents can lead to renal vasoconstriction as well as direct tubule cell injury. Contrast-induced nephropathy usually manifests as an increase in serum creatinine 1-2 days following exposure; most patients are not oliguric. In most cases, the serum creatinine normalizes in the next 3-7 days, and treatment is supportive. The overall risk of radiocontrast agents to cause acute kidney injury remains controversial but appears to be low in children with normal kidney function and with the dominant current practice of using low osmolar contrast agents. Biologic nephrotoxins include venomous exposures from insects, reptiles, amphibians, and a wide variety of sea-dwelling animals. The most common forms of toxic nephropathy unfortunately relate to the exposure of children to pharmacologic agents, accounting for close to 20% of episodes of acute kidney injury occurring in children and adolescents. Age, underlying medical condition, genetics, exposure dose, and the concomitant use of other drugs all influence the likelihood of developing acute kidney injury. One common scenario is the use of nonsteroidal antiinflammatory agents (NSAIDs) in febrile children with concomitant dehydration. In this situation, NSAIDs can inhibit the production of intrarenal vasodilatory prostaglandins, thereby leading to decreased renal perfusion and acute kidney injury.

Table 560.3 summarizes the agents that commonly cause acute kidney injury and some of their clinical manifestations. A combination of multiple drugs amplifies the risk. Mechanisms of injury often help to explain the presentation; however, multiple toxic exposures in patients with complicated clinical histories often limit the ability to clearly establish clinical cause and effect. For example, diminished urine output may be the clinical hallmark of tubular obstruction caused by agents such as methotrexate or agents that cause acute tubular necrosis, such as amphotericin B or pentamidine. Alternatively, nephrogenic

Table 560.3 Renal Syndromes Produced by Nephrotoxins

NEPHROTIC SYNDROME
- Angiotensin-converting enzyme inhibitors
- Gold salts
- Interferon
- Mercury compounds
- Nonsteroidal antiinflammatory drugs
- Penicillamine

NEPHROGENIC DIABETES INSIPIDUS
- Amphotericin B
- Cisplatin
- Colchicine
- Demeclocycline
- Lithium
- Methoxyflurane
- Propoxyphene
- Vinblastine

RENAL VASCULITIS
- Hydralazine
- Isoniazid
- Penicillins
- Propylthiouracil
- Sulfonamides
- Numerous other drugs that can cause a hypersensitivity reaction

THROMBOTIC MICROANGIOPATHY
- Cyclosporine A
- Oral contraceptive agents
- Mitomycin C

NEPHROCALCINOSIS OR NEPHROLITHIASIS
- Allopurinol
- Bumetanide
- Ethylene glycol
- Furosemide
- Melamine
- Methoxyflurane
- Topiramate
- Vitamin D

ACUTE KIDNEY INJURY
- Acetaminophen
- Acyclovir
- Aminoglycosides
- Amphotericin B
- Angiotensin-converting enzyme inhibitors
- Biologic toxins (snake, spider, bee, wasp)
- Cisplatin
- Cyclosporine
- Ethylene glycol
- Halothane
- Heavy metals
- Ifosfamide
- Lithium
- Methoxyflurane
- Nonsteroidal antiinflammatory drugs
- Radiocontrast agents
- Tacrolimus
- Vancomycin with or without piperacillin-tazobactam

OBSTRUCTIVE UROPATHY
- Sulfonamides
- Acyclovir
- Methotrexate
- Protease inhibitors
- Ethylene glycol
- Methoxyflurane

FANCONI SYNDROME
- Aminoglycosides
- Chinese herbs (aristolochic)
- Cisplatin
- Heavy metals (cadmium, lead, mercury, and uranium)
- Ifosfamide
- Lysol
- Outdated tetracycline

RENAL TUBULAR ACIDOSIS
- Amphotericin B
- Lead
- Lithium
- Toluene

INTERSTITIAL NEPHRITIS
- Amidopyrine
- *p*-Aminosalicylate
- Carbon tetrachloride
- Cephalosporins
- Cimetidine
- Cisplatin
- Colistin
- Copper
- Cyclosporine
- Ethylene glycol
- Foscarnet
- Gentamicin
- Gold salts
- Indomethacin
- Interferon-α
- Iron
- Kanamycin
- Lithium
- Mannitol
- Mercury salts
- Mitomycin C
- Neomycin
- Nonsteroidal antiinflammatory drugs
- Penicillins (especially methicillin)
- Pentamidine
- Phenacetin
- Phenylbutazone
- Poisonous mushrooms
- Polymyxin B
- Radiocontrast agents
- Rifampin
- Salicylate
- Streptomycin
- Sulfonamides
- Tacrolimus
- Tetrachloroethylene
- Trimethoprim-sulfamethoxazole

STEC, Shiga toxin–producing *Escherichia coli*.

diabetes insipidus may be the critical clinical manifestation of agents that cause interstitial nephritis, such as lithium or cisplatin. Acute kidney injury due to nephrotoxins is frequently polyuric. Nephrotoxicity is often reversible if the noxious agent is promptly removed.

Clinical use of potential nephrotoxins should be judicious. Necessity of exposure, dosing parameters, and the use of drug levels or pharmacogenomic data, when available, should always be considered. Caution is particularly mandated for patients with complex medical conditions that include preexisting renal disease, cardiac disease, diabetes, and/or complicated surgeries. Alternative approaches to imaging or the use of different pharmacologic options should be considered when possible. Imaging modalities such as ultrasonography, radionuclide scanning, or MRI may be preferable to contrast studies in some patients. Alternatively, a judicious volume expansion with or without the administration of *N*-acetylcysteine might offer renoprotection when radioiodinated contrast studies are critical, especially in children with chronic kidney disease or those who are already on other nephrotoxic agents. Pharmacologic agents with no known kidney effects can often be substituted for known nephrotoxins with equal clinical efficacy. In all cases, simultaneous use of known nephrotoxins should be avoided whenever possible. The use of nephrotoxic agents represents one of the few modifiable risk factors for acute kidney injury, and promising new biomarkers for the early detection and modification of nephrotoxic injuries are currently becoming available. Use of the electronic health record for systematic surveillance for nephrotoxic medication exposure and acute kidney injury can also lead to sustained reductions in avoidable kidney injury.

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560.7 Cortical Necrosis

Prasad Devarajan

BACKGROUND

Renal cortical necrosis is a rare cause of severe acute kidney injury occurring secondary to extensive ischemic damage of the renal cortex. Ischemic necrosis is due to markedly decreased renal arterial perfusion as a result of vascular spasm, microvascular injury, or intravascular coagulation. Renal cortical necrosis is usually bilateral and extensive, although focal and patchy forms have also been described. The medulla, the juxtamedullary cortex, and a thin rim of subcapsular cortex are usually spared. It occurs most commonly in neonates and in adolescents of childbearing age.

ETIOLOGY

In newborns, cortical necrosis is most associated with hypoxic or ischemic insults caused by perinatal asphyxia, placental abruption, and twin–twin or fetal–maternal transfusion. Other causes include renal vascular thrombosis and severe congenital heart disease. After the neonatal period, cortical necrosis is most commonly seen in children with septic shock or severe hemolytic-uremic syndrome. In adolescents and women, cortical necrosis occurs in association with obstetric complications, including prolonged intrauterine fetal death, placental abruption, septic abortion, or amniotic fluid embolism.

Less common causes of cortical necrosis include malaria, extensive burns, snakebites, infectious endocarditis, and medications (e.g., nonsteroidal antiinflammatory agents). Acute renal cortical necrosis has also been reported to occur in SLE-associated antiphospholipid antibody syndrome.

PATHOGENESIS

The presumed initiating factor in many cases is intense vasospasm of the small vessels. When prolonged, this leads to necrosis and thrombosis of the distal arterioles and glomeruli, with ensuing cortical necrosis. In hemolytic-uremic syndrome and septic abortion, endotoxin-mediated endothelial damage contributes to worsening vascular thrombosis.

CLINICAL MANIFESTATIONS

Cortical necrosis clinically presents as severe acute kidney injury in patients with predisposing causes. Urine output is diminished and gross, and/or microscopic hematuria may be present. Hypertension is common, and thrombocytopenia may be present because of renal microvascular injury.

LABORATORY AND RADIOLOGIC FINDINGS

Laboratory results are consistent with acute kidney injury: an elevated BUN and creatinine, hyperkalemia, and metabolic acidosis. Anemia and thrombocytopenia are common. Urinalysis reveals hematuria with red cell or granular casts, and proteinuria.

Ultrasound examination with Doppler flow studies demonstrates decreased perfusion to both kidneys. Kidneys are enlarged in the initial stages, but cortical tissue becomes shrunken in the later stages. Thin cortical shells of calcification (tram lines) are a radiologic hallmark, but they develop only 4-5 weeks after the initial insult.

CT scanning with contrast is the most sensitive imaging modality in renal cortical necrosis. Diagnostic features include absent opacification of the renal cortex and enhancement of subcapsular and juxtamedullary regions and of the medulla with absent excretion of contrast medium.

A radionuclide renal scan shows decreased uptake with significantly delayed or absent function. Renal scanning is the imaging technique of choice if contrast-enhanced CT scanning is not available or is contraindicated.

TREATMENT

The cornerstones of therapy for renal cortical necrosis are to restore hemodynamic stability, institute early dialysis, and treat the underlying cause. Most cases of renal cortical necrosis require initial treatment in an intensive care setting. It is important to prevent or treat the underlying cause of acute cortical necrosis, when possible. Therapy involves medical management of acute renal failure, often with the initiation of dialysis as indicated. Management is otherwise supportive and involves volume repletion, correction of asphyxia, and treatment of sepsis.

PROGNOSIS

The most important prognostic factors include the extent of necrosis, duration of oligoanuria, and severity of the overall associated conditions. Untreated, renal cortical necrosis has a high mortality rate, exceeding 50%. Early initiation of dialysis significantly diminishes the mortality rate. Most patients require dialysis for variable but extended periods of time. Twenty to 40% of patients have partial recovery of renal function, the extent of which depends on the amount of preserved cortical tissue. All patients require long-term follow-up for chronic kidney disease.

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560.8 Coagulopathies and Thrombocytopenia

Prasad Devarajan

Gross or microscopic hematuria may be associated with inherited or acquired disorders of coagulation (hemophilia, disseminated intravascular coagulation, thrombocytopenia). In these cases, however, hematuria is not usually the presenting complaint or a major factor affecting the clinical management or outcome (see Chapters 524-533).

Chapter 561

Tubulointerstitial Disease Associated with Hematuria

Prasad Devarajan

Gross or microscopic hematuria may be associated with several disorders of the renal tubules and the interstitium (pyelonephritis, tubulointerstitial nephritis, papillary necrosis, acute tubular necrosis). However, except for papillary necrosis, hematuria is not usually the presenting complaint or a major factor affecting the clinical management or outcome (see Chapters 561.2-561.4).

561.1 Pyelonephritis

See Chapter 575, Urinary Tract Infections.

561.2 Tubulointerstitial Nephritis

Prasad Devarajan

Tubulointerstitial nephritis (TIN, also called interstitial nephritis) is the term applied to conditions characterized by tubulointerstitial inflammation and damage with relative sparing of glomeruli and vessels. Both acute and chronic primary forms exist. **Acute TIN** is characterized by an acute extensive lymphocytic inflammatory response and a rapid decline in renal function. **Chronic TIN** usually displays a protracted onset and a chronic patchy lymphocytic infiltrate, interstitial fibrosis, and a slow deterioration in renal function. Secondary forms of interstitial nephritis can be associated with primary glomerular diseases, as well as systemic diseases affecting the kidney.

ACUTE TUBULOINTERSTITIAL NEPHRITIS

The hallmarks of acute TIN are an extensive lymphocytic infiltration of the tubulointerstitium, interstitial edema, and varying degrees of tubular necrosis and regeneration. Eosinophils may be present, particularly in drug-induced TIN; occasionally, interstitial granulomas with giant cells occur. Glomeruli are usually normal in primary TIN. The pathogenesis is not fully understood, but a T-cell–mediated immune mechanism has been postulated. *Drugs are the most common cause of acute TIN in children.* Many medications, especially antimicrobials, anticonvulsants, and analgesics, have been implicated as etiologic agents (Table 561.1). Nonsteroidal antiinflammatory drugs (NSAIDs), penicillins, and sulfonamides account for most cases. Drug-induced TIN is an idiosyncratic reaction that occurs in only a very small subset of patients who ingest the medication, typically with repeated exposure. Drugs of abuse (including synthetic cannabinoids, bath salts, ecstasy, anabolic steroids, inhaled solvents, heroin, and cocaine) are an increasingly common problem in certain populations. Other causes of acute TIN include infections, primary glomerular diseases, and systemic diseases such as systemic lupus erythematosus.

Clinical Manifestations

The classic presentation of acute TIN is fever, rash, and arthralgia in the setting of a rising serum creatinine. Acute TIN accounts for about 5% of pediatric acute kidney injury cases. Although the full clinical triad may be noted in drug-induced TIN, most patients with acute TIN do not demonstrate all the typical features. The rash can vary from maculopapular to urticarial and is often transient. Patients often have nonspecific constitutional symptoms of nausea, vomiting, fatigue, and weight loss. Flank pain may be present, presumably secondary to stretching of the renal capsule from acute inflammatory enlargement of the kidney. If acute TIN is caused by a systemic disease such as systemic lupus erythematosus, the clinical presentation will be consistent with specific signs and symptoms of the underlying disease. Unlike the typical presentation of oliguric **acute kidney injury (AKI)** seen with glomerular diseases, 30–40% of patients with acute TIN are nonoliguric, and hypertension is less common. Peripheral eosinophilia can occur, especially with drug-induced TIN. Microscopic hematuria is invariably present, but significant hematuria or proteinuria >1.5 g/day is uncommon. One exception is patients whose TIN is caused by NSAIDs, who can present with nephrotic syndrome. Urinalysis can reveal white blood cell, granular, or hyaline casts, but red blood cell casts (a characteristic of glomerular disease) are absent. The presence of urine eosinophils is neither sensitive nor specific, being detected in only 25% of cases. Because of pyuria, the initial diagnosis may be a urinary tract infection.

Diagnosis

The diagnosis is usually based on the clinical presentation and laboratory findings. A renal biopsy will establish the correct diagnosis in cases where the etiology or clinical course confounds the diagnosis. A careful history of the timing of disease onset in relation to drug exposure is essential in suspected drug-induced TIN. Because of the immune-mediated nature of TIN, signs or symptoms generally appear within 1-2 weeks following exposure. In children, antimicrobials are a common inciting agent. NSAIDs are an important cause of acute TIN in children, and volume depletion or underlying chronic kidney disease can increase the risk of occurrence. Urinalysis and serial measurements of serum creatinine and electrolytes should be monitored. Renal ultrasonography, though not diagnostic, can demonstrate enlarged, echogenic kidneys. Removal of a suspected offending agent followed by spontaneous improvement in kidney function is highly suggestive of the diagnosis, and additional testing is generally not performed in this setting. In more severe cases, in which the cause is unclear, or the patient's kidney function deteriorates rapidly, a renal biopsy is indicated.

Treatment and Prognosis

Treatment of acute TIN starts with eliminating the suspected causative drug or agent. Most patients with mild ATN recover kidney function when the inciting agent is discontinued. Other treatment includes supportive care directed at addressing complications of AKI, such as hyperkalemia or volume overload (see Chapter 572.1). Corticosteroid administration within 2 weeks of the discontinuation of certain offending agents (e.g., NSAIDs or antibiotics) can hasten the recovery and improve the long-term prognosis in drug-induced TIN. Current recommendations favor the use of oral prednisone in children whose kidney function fails to improve soon after stopping the suspected agent. IV methylprednisolone is used in severe cases. Mycophenolate mofetil has been found to be beneficial in steroid-unresponsive cases. Whether such therapies are indicated in other causes of TIN is not clear. For patients with prolonged kidney insufficiency, the prognosis remains guarded, and severe acute TIN from any cause can progress to chronic TIN.

CHRONIC TUBULOINTERSTITIAL NEPHRITIS

In children, chronic TIN most commonly occurs in the context of (1) an underlying congenital urologic kidney disease, such as obstructive uropathy or vesicoureteral reflux, or (2) an underlying metabolic disorder affecting the kidneys (see Table 561.1). Some commonly used drugs such as cyclosporine and tacrolimus also cause chronic TIN. Chronic TIN can occur as an idiopathic disease, although this is more common in adults.

The **juvenile nephronophthisis (JN)–medullary cystic kidney disease complex (MCKD)** is a group of inherited, genetically determined cystic renal diseases that share the common histologic finding of chronic TIN. At least 20 different genes are associated with JN, usually

Table 561.1 Etiology of Interstitial Nephritis

ACUTE INTERSTITIAL NEPHRITIS

Drugs

- **Antimicrobials**
  - Penicillin derivatives
  - Cephalosporins
  - Sulfonamides
  - Trimethoprim-sulfamethoxazole
  - Ciprofloxacin
  - Tetracyclines
  - Vancomycin
  - Erythromycin derivatives
  - Rifampin
  - Amphotericin B
  - Acyclovir
- **Anticonvulsants**
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Sodium valproate

Drugs of Abuse

- Synthetic cannabinoids
- Bath salts
- Ecstasy
- Anabolic steroids
- Inhaled solvents
- Heroin
- Cocaine

Other Drugs

- Allopurinol
- All-trans-retinoic acid
- 5-Aminosalicylic acid
- Cimetidine
- Cyclosporine
- Diuretics
- Escitalopram
- Interferon
- Mesalazine
- Quetiapine
- Olanzapine
- Nonsteroidal antiinflammatory drugs
- Protease inhibitors
- Proton pump inhibitors
- Aristolochic acid (traditional Chinese herb)

Infections

- Adenovirus
- Bacteria associated with acute pyelonephritis
- BK virus
- *Brucella*
- Streptococcal species
- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis B virus
- Histoplasmosis
- Human immunodeficiency virus
- Hantavirus
- Leptospirosis
- *Toxoplasma gondii*

Disease-Associated

- Glomerulonephritis (e.g., systemic lupus erythematosus)
- Acute allograft rejection
- Tubulointerstitial nephritis and uveitis (TINU) syndrome

Idiopathic

CHRONIC INTERSTITIAL NEPHRITIS

Drugs and Toxins

- Analgesics
- Cyclosporine
- Lithium
- Heavy metals (including lead)

Infections (See Acute Interstitial Nephritis)

- **Disease-associated causes**
  - Metabolic and hereditary
  - Cystinosis
  - Oxalosis
  - Fabry disease
  - Wilson disease
  - Sickle cell nephropathy
  - Alport syndrome
  - Juvenile nephronophthisis, medullary cystic disease

Immunologic

- Systemic lupus erythematosus
- Crohn disease
- Chronic allograft rejection
- Tubulointerstitial nephritis and uveitis (TINU) syndrome
- Anti-tubular basement disease

Urologic

- Posterior urethral valves
- Eagle-Barrett syndrome
- Ureteropelvic junction obstruction
- Vesicoureteral reflux

Miscellaneous

- Balkan nephropathy
- Radiation
- Sarcoidosis
- Neoplasm

Idiopathic

inherited as an autosomal recessive disease (Table 561.2). These genes only define 30% of cases, and new genes are being identified at a rapid pace. Although uncommon in the United States, JN causes 10–20% of pediatric cases of end-stage kidney disease (ESKD) in Europe. Patients with JN typically present with polyuria, growth failure, unexplained anemia, and chronic kidney disease in late childhood or adolescence.

JN is a **ciliopathy** and is often associated with extrarenal features such as retinal degeneration, hepatobiliary disease, cerebellar vermis hypoplasia, laterality defects, intellectual disability, and shortening of bones (see Chapter 101.3). These features are represented in several syndromes, such as **Senior-Løken syndrome (retinitis pigmentosa), Joubert syndrome (cerebellar vermis hypoplasia;** 22 subtypes),

Table 561.2 Juvenile Nephronophthisis: Summary of the *NPHP1* to *NPHP18, NHPH1L,* and *NPHP2L* Genes, Gene Products, Chromosomal Localization, Phenotypes, Extrarenal Symptoms, and Interaction Partners

GENE (PROTEIN)	CHROMOSOME	PHENOTYPE (MEDIAN AGE AT ESRD)	EXTRARENAL SYMPTOMS	INTERACTION PARTNERS
NPHP1 (nephrocystin-1)	2q13	NPHP (13 yr)	RP (10%), OMA (2%), JBTS (rarely)	Inversin, nephrocystin-3, nephrocystin-4, filamin A and B, tensin, β-tubulin, PTK2B
NPHP2/INVS (inversin)	9q31	Infantile NPHP (<4 yr)	RP (10%), LF, situs inversus, CHD	Nephrocystin-1, calmodulin, catenins, β-tubulin, APC2
NPHP3 (nephrocystin-3)	3q22	Infantile and adolescent NPHP	LF, RP (10%), situs inversus, MKS, CHD	Nephrocystin-1
NPHP4 (nephrocystin-4)	1p36	NPHP (21 yr)	RP (10%), OMA, LF	Nephrocystin-1, BCAR1, PTK2B
NPHP5/IQCB1 (nephrocystin-5)	3q21	NPHP (13 yr)	Early-onset RP	Calmodulin, RPGR, nephrocystin-6
NPHP6/CEP290 (nephrocystin-6/CEP290)	12q21	NPHP	JBTS, MKS	ATF4, nephrocystin-5, CC2D2A
NPHP7/GLIS2 (nephrocystin-7/GLIS2)	16p	NPHP	—	—
NPHP8/RPGRIP1L (nephrocystin-8/RPGRIP1L)	16q	NPHP	JBTS, MKS	Nephrocystin-1
NPHP9/NEK8 (nephrocystin-9/NEK8)	17q11	Infantile NPHP	—	—
NPHP10/SDCCAG8 (nephrocystin-10/SDCCAG8)	1q43	Juvenile NPHP	RP (SLS), BBS-like	OFD1
TMEM67/MKS3/NPHP11 (nephrocystin-11/meckelin)	8q22.1	NPHP	JBTS, MKS, LF	MKS1, nephrocystin-1, nephrocystin-4, nephrocystin-6, nesprin-2, TMEM216
TTC21B//JBTS11/NPHP12 (nephrocystin-12/IFT139)	2q24.3	Early-onset NPHP, juvenile NPHP	JATD, MKS, JBTS, BBS-like	Ciliopathy modifier
WDR19/NPHP13 (nephrocystin-13/IFT144)	4p14	NPHP	JATD, SBS, CED, RP, Caroli, BBS-like	—
ZNF423/NPHP14 (nephrocystin-14/ZNF423)	16q12.1	Infantile NPHP, PKD	JBTS, situs inversus	PARP1, nephrocystin-6,
CEP164/NPHP15 (nephrocystin-15 centrosomal protein 164 kDa)	11q23.3	NPHP (8 years)	RP, JBTS, LF, obesity	ATRIP, CCDC92, TTBK2, nephrocystin-3, nephrocystin-4, Dvl3
ANKS6/NPHP16 (nephrocystin-16/ANKS6)	9q22.33	NPHP, PKD	LF, situs inversus, cardiovascular abnormalities	INVS, nephrocystin-3, NEK8, HIF1AN, NEK7, BICC1
IFT172/NPHP17 (nephrocystin-17/IFT172)	2p23.3	NPHP	JATD, MZSDS, JBTS	IFT140, IFT80
CEP83/NPHP18 (nephrocystin-18/centrosomal protein 83 kDa)	12q22	Early-onset NPHP (3 yr)	Learning disability, hydrocephalus, LF	CEP164, IFT20
NPHP1L/XPNPEP3 (nephrocystin-1L/XPNPEP3)	22q13	NPHP	Cardiomyopathy, seizures	Cleaves LRRC50, ALMS1, nephrocystin-6
NPHP2L/SLC41A1 (nephrocystin-2L/SLC41A1)	1q32.1	NPHP	Bronchiectasis	—

ATF4, Activating transcription factor 4; APC2, anaphase-promoting complex 2; BBS, Bardet-Biedl syndrome; BCAR1, breast cancer antiestrogen resistance 1; CC2D2A, coiled-coil and C2 domain containing 2A; CED, cranioectodermal dysplasia; CHD, congenital heart disease; JATD, Jeune asphyxiating thoracic dysplasia; JBTS, Joubert syndrome; LF, liver fibrosis; MKS, Meckel-Gruber syndrome; MZSDS, Mainzer-Saldino syndrome; NPHP, nephronophthisis; OMA, oculomotor apraxia; PKD, polycystic kidney disease; PTK2B, protein tyrosine kinase 2B; RP, retinitis pigmentosa; RPGR, retinitis pigmentosa GTPase regulator; SBS, Sensenbrenner syndrome; SLS, Senior-Løken syndrome.

From Wolf MTF. Nephronophthisis and related syndromes. *Curr Opin Pediatr.* 2015;27:201–211. Table 1.

Bardet-Biedl syndrome (intellectual disability, obesity; 17 subtypes), **Jeune asphyxiating thoracic dystrophy** (shortening of the long bones, narrow rib cage; 11 subtypes), and many others. **MCKD** is an autosomal dominant disease that typically manifests in adulthood, characterized by tubulointerstitial sclerosis leading to ESKD. Because at least four different gene pathogenic variants may give rise to the condition, the name **autosomal dominant tubulointerstitial kidney disease (ADTKD)** has been proposed for this condition. The two best known forms of ADTKD include mucin-1 kidney disease 1 (MKD1) and mucin-2 kidney disease/uromodulin kidney disease (MKD2), based on the pathogenic variant identified. **TIN with uveitis (TINU syndrome)** is a rare autoimmune syndrome of chronic TIN with bilateral anterior uveitis and bone marrow granulomas that occurs primarily in adolescent girls. Clinical manifestations include photophobia, ocular pain and redness, and visual impairment. Chronic TIN is seen in all forms of progressive kidney disease, regardless of the underlying cause, and the severity of interstitial disease is the single most important factor predicting progression to ESKD.

Pathogenesis and Pathology

The pathophysiology of chronic TIN is undefined, but data suggest that, other than the abnormal cilia structure and function in JN and MCKD, in other cases it is immune mediated. Cells making up the interstitial infiltrate appear to be a combination of native interstitial cells, inflammatory cells recruited from the circulation, and resident tubular cells that undergo epithelial-mesenchymal transformation. Grossly, kidneys can appear pale and small for age. Microscopically, tubular atrophy and "dropout" with interstitial fibrosis and a patchy lymphocytic interstitial inflammation are seen. Patients with JN often have characteristic small cysts in the corticomedullary region. In primary chronic TIN, glomeruli are relatively spared until late in the disease course. Patients with chronic TIN secondary to a primary glomerular disease have histologic evidence of the primary disease. Chronic TIN due to cyclosporine or tacrolimus use is characterized by tubular atrophy, "stripe" interstitial fibrosis, and vascular sclerosis.

Clinical Manifestations

The clinical features of chronic TIN are often nonspecific and can reflect signs and symptoms of slowly progressive chronic kidney disease (see Chapter 572). Fatigue, growth failure, polyuria, polydipsia, and enuresis are often present. Anemia that is seemingly disproportionate to the degree of kidney insufficiency is common and is a particularly prominent feature in JN. Because tubular damage often leads to salt wasting by the kidney, significant hypertension is unusual. Fanconi syndrome, proximal renal tubular acidosis, distal renal tubular acidosis, and hyperkalemic distal renal tubular acidosis can occur.

Extrarenal manifestations of **nephronophthisis** include ophthalmic, neurologic, hepatic, and skeletal disorders (Table 561.3).

Table 561.3 Extrarenal Manifestations Associated with Nephronophthisis and Resulting Syndromes Associated with *NPHP* Pathogenic Variants

DISORDER	SYNDROME
OPHTHALMOLOGIC	
Retinitis pigmentosa	Senior-Løken syndrome (SLSN)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Alstrom (RP, obesity, DM type 2, hearing impairment)
	RHYNS (RP, hypopituitarism, skeletal dysplasia)
Oculomotor apraxia	Cogan syndrome
Nystagmus	Joubert syndrome/Joubert syndrome–related disorders
Coloboma	Joubert syndrome/Joubert syndrome–related disorders
NEUROLOGIC	
Encephalocele	Meckel-Gruber syndrome (occipital encephalocele, NPHP)
Vermis aplasia	Joubert syndrome/Joubert syndrome–related disorders
Hypopituitarism	RHYNS
HEPATIC	
Liver fibrosis	Boichis syndrome
	Meckel-Gruber syndrome (occipital encephalocele, NPHP)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Joubert syndrome/Joubert syndrome–related disorders
SKELETAL	
Short ribs	Jeune syndrome/asphyxiating thoracic dystrophy
Cone-shaped epiphysis	Mainzer-Saldino syndrome
Postaxial polydactyly	Joubert syndrome/Joubert syndrome–related disorders
	Bardet-Biedl syndrome (NPHP, RP, obesity, deafness)
	Ellis van Creveld
Skeletal abnormalities	Sensenbrenner syndrome/ cranioectodermal dysplasia
	Ellis van Creveld
OTHERS	
Situs inversus	
Cardiac malformation	
Bronchiectasis	
Ulcerative colitis	

RP, Retinitis pigmentosa; DM, diabetes mellitus; NPHP, nephronophthisis.
From Wolf MT, Hildebrandt F. Nephronophthisis. *Pediatr Nephrol*. 2011;26:181–194.

Diagnosis

The diagnosis is suggested by signs or symptoms of kidney tubular damage such as polyuria and an elevated serum creatinine value, coupled with a history suggestive of a chronic disease, such as long-standing enuresis or the presence of anemia resistant to iron therapy. Radiographic studies, in particular ultrasonography, can give additional evidence of chronicity, such as small, echogenic kidneys, corticomedullary microcysts suggesting JN, or findings of obstructive uropathy. A voiding cystourethrogram can demonstrate the presence of vesicoureteral reflux or bladder abnormalities. If JN is suspected, a specific genetic diagnosis is available. In instances in which the cause is unclear, a kidney biopsy may be performed. In cases of advanced disease, a kidney biopsy might not be diagnostic. Many ESKDs display a common histologic appearance of tubular fibrosis and inflammation.

Treatment and Prognosis

Therapy is directed at maintaining the fluid and electrolyte balance and avoiding further exposure to nephrotoxic agents. Patients with obstructive uropathies can require salt supplementation and treatment with potassium-binding resin. Prevention of infection by antibiotic prophylaxis can slow the progression of renal damage in appropriate patients. The prognosis in patients with chronic TIN depends in large part on the nature of the underlying disease. Patients with obstructive uropathy or vesicoureteral reflux can have a variable degree of kidney damage and thus a variable course. ESKD can develop over months to years. Patients with JN uniformly progress to ESKD by adolescence. Patients with metabolic disorders can benefit from treatment when available.

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561.3 Papillary Necrosis

Prasad Devarajan

Renal papillary necrosis (RPN) is a descriptive term applied to conditions that result in necrosis of the kidney medullary pyramids and papillae. The hypoxic and hypertonic environment that normally prevails in the kidney medullary region renders it especially vulnerable to ischemic necrosis. Common precipitating factors in children include shock, hypovolemia, hypoxia, pyelonephritis, urinary tract obstruction, and sickle cell hemoglobinopathies, Analgesic abuse and diabetes mellitus are additional important causes in adults. RPN can result in secondary infection, deposition of stones, and sloughing of papillae with resultant urinary tract obstruction. Both an acute progressive clinical course and a more chronic protracted form have been described. Patients most commonly present with flank pain and hematuria. Radiologic studies are key to establishing the diagnosis. Management is directed toward treating the underlying cause, ameliorating kidney ischemia with hydration, and surgical relief of obstruction.

PATHOGENESIS AND PATHOLOGY

RPN may be focal (involving only the papillary tips) or diffuse (involving the whole papilla and the innermost areas of the medulla). RPN may affect a single papilla or multiple papillae. Histologically, the tissue typically reveals classic coagulative necrosis, surrounded by an inflammatory response.

Under normal conditions, the medullary region of the kidney subsists on a hypoxic precipice due to low blood flow and countercurrent exchange of oxygen, although paradoxically housing nephron segments with very high energy requirements. The blood flow decreases even further as one approaches the innermost regions of the medulla and becomes marginal toward the apex and tips of the papillae. The already compromised blood supply is further attenuated in several pathophysiologic states, including the hypoxia from shock and dehydration, the intraluminal stasis of sickle cell nephropathy, the inflammation of pyelonephritis, the increased pressure of urinary tract obstruction, the microvascular changes of diabetes, and the direct damage from analgesics (including NSAIDs). Approximately 15–30% of patients with sickle cell disease will encounter episodes of RPN during their lifetime.

CLINICAL MANIFESTATIONS

The classic presentation of acute RPN is flank pain and renal colic, gross hematuria with clots and tissue debris, and fever with chills. AKI, an increase in the serum creatinine, and oliguria are not common but may accompany the rapidly progressive form. Patients with the chronic indolent form may be asymptomatic and may first present with the passage of sloughed papillae in the urine.

DIAGNOSIS

The diagnosis of RPN is usually based on the history, clinical presentation, laboratory findings, and radiologic investigations. Contrast-enhanced CT scanning is the imaging modality of choice. In the acute phase, this method depicts several typical features, including clefts in the medulla, pelvic filling defects, nonenhanced lesions surrounded by rings of excreted material, medullary calcifications, and the presence of obstruction. If IV contrast is contraindicated, CT scanning without contrast or renal ultrasonography may be performed. These modalities are now replacing IV urography, which was the imaging method of choice in the past.

TREATMENT AND PROGNOSIS

Treatment of acute RPN starts with ameliorating the kidney ischemia with IV hydration. In addition, it is important to treat the underlying cause, including appropriate medical management of shock, sepsis, pyelonephritis, or sickle cell disease. Cessation of any analgesics (including NSAIDs) is critical. Patients with acute obstruction may require surgical intervention for relief.

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561.4 Acute Tubular Necrosis

Prasad Devarajan

Acute tubular necrosis (ATN) is a descriptive term applied to conditions that result in necrosis of the renal tubular epithelial cells. The hypoxic environment that normally prevails in the kidney medullary region renders its nephron segments especially vulnerable to necrotic cell death. ATN frequently coexists with other forms of cell death, as well as cellular regeneration. Common precipitating factors in children include prolonged renal ischemia, sepsis, shock, hypovolemia, and nephrotoxic medications. ATN is the most common cause of *intrinsic* **acute kidney injury (AKI)** (see Chapter 572). ATN is clinically characterized by a rapid (within hours to days) decline in kidney function that leads to retention of waste products such as BUN and creatinine, fluid overload, and reduced urine output in many cases. Patients with hospital-acquired ATN frequently have no specific symptoms, and the diagnosis requires a high index of suspicion in predisposed individuals. Laboratory tests and radiologic studies are the key to establishing the diagnosis. Management is directed toward treating the underlying or precipitating cause, correction of imbalances in fluid, electrolyte, and acid-base status, avoidance of nephrotoxic medications, and treatment of complications.

PATHOGENESIS AND PATHOLOGY

The pathologic findings are highly variable, depending on the etiology and the region of the kidney affected. In children with predominantly ischemic ATN, necrosis is relatively inconspicuous, whereas it is more widespread in nephrotoxic ATN. Because the medullary region of the kidney (including the straight segment of the proximal tubule and the medullary thick ascending limb of the loop of Henle) normally subsists in a hypoxic environment due to low blood flow and countercurrent exchange of oxygen, these nephron segments are usually the most severely affected. Typical findings include patchy areas of tubule cell necrosis with resultant loss of tubule epithelial cells and exposure of denuded basement membrane. Other forms of cell death, including apoptosis, necroptosis, and ferroptosis, occur simultaneously. Surviving proximal tubule cells show diffuse effacement and loss of the brush border and apical blebs. The distal nephron segments exhibit tubular dilatation with intraluminal casts. There is concomitant evidence for cellular regeneration and repair among freshly damaged tubule epithelial cells. Injury is aggravated by several pathophysiologic states, including the ischemia from sepsis, shock, and dehydration and the direct damage from nephrotoxic medications.

The significant decline in kidney function is often out of proportion to the observed patchy histologic changes. In addition to tubule cell necrosis, several other factors contribute to the decline in the glomerular filtration rate (GFR). First, a single collecting tubule drains multiple nephrons, such that obstruction of even a small number of collecting tubules results in failure of filtration from several nephrons. Second, obstruction aggravates the backflow of filtered tubular fluid into the vascular space across the denuded epithelium. Third, loss of the proximal tubular reabsorptive capacity results in increased delivery of sodium chloride to the macula densa, with activation of the tubuloglomerular feedback mechanisms that worsens the afferent arteriolar constriction. Fourth, many additional factors contribute to the pathogenesis of ATN, including changes in the microvascular blood flow, endothelial damage, and the activation of inflammatory pathways.

The pathophysiology and clinical course of ATN may be divided into three sequential phases, namely, initiation, maintenance, and recovery. The *initiation* phase occurs during the initial exposure to ischemia or nephrotoxins. Tubule cell damage begins to evolve, and the sloughed tubular cell debris results in obstruction of the tubular lumen. The combination of hypoperfusion and obstruction to the tubular fluid flow results in a fall in the GFR and urine output and a rise in serum creatinine levels. During the *maintenance* phase of ATN, renal tubule injury is established at its highest severity, the GFR and urine output become stabilized at a very low level, and the BUN and serum creatinine peak. It should be noted that ATN due to nephrotoxic

medications is typically nonoliguric. This phase typically lasts for 1-2 weeks but may extend to several weeks. Complications (e.g., metabolic, fluid, and electrolyte imbalances) typically occur during this phase. The *recovery* phase, also called the diuretic phase, is characterized by regeneration of lost tubule epithelial cells, repair of sub-lethally injured cells, and removal of intratubular casts by reestablishment of tubular fluid flow. It is clinically heralded by polyuria and a slow recovery of the GFR. Diuresis occurs because the rapidly increasing GFR precedes the complete recovery of the tubule cell structure and function and can result in volume depletion if not recognized and treated promptly.

The most prevalent causes of ATN in neonates and older children are shown in Tables 561.4 and 561.5, respectively.

CLINICAL MANIFESTATIONS

ATN is largely asymptomatic, and the clinical diagnosis depends on having a high index of suspicion in children with etiologic risk factors. ATN most frequently manifests with a progressive accumulation of fluid, a serial elevation in the BUN and serum creatinine, and a reduction in urine output, in a predisposed patient who has been exposed to either ischemic or nephrotoxic injury. The evaluation requires a complete history directed toward the known causes of ATN, physical examination, laboratory testing, and renal imaging. A detailed history of all ingested drugs and medications is especially important. Although ATN is technically a histologic diagnosis, kidney biopsies are only rarely performed in children with this condition.

Signs of ATN on physical examination include edema, hypertension, and evidence of heart failure. Children with intravascular volume depletion exhibit tachycardia, hypotension, decreased skin turgor, and dry mucous membranes.

Table 561.4 Prevalent Causes of Acute Tubular Necrosis in Neonates

MECHANISM	CAUSES
Ischemia	Perinatal asphyxia, respiratory distress syndrome, hemorrhage, congenital heart disease, sepsis, shock
Exogenous toxins	Aminoglycosides, maternal ingestion of angiotensin-converting enzyme inhibitors or nonsteroidal antiinflammatory drugs
Endogenous toxins	Hemoglobin (hemolysis), myoglobin (seizures)
Primary kidney disease	Renal vein thrombosis, renal artery thrombosis, polycystic kidney disease

Table 561.5 Prevalent Causes of Acute Tubular Necrosis in Older Children

MECHANISM	CAUSES
Ischemia	Severe dehydration, hemorrhage, shock, sepsis, burns, major surgery, severe cardiac disease, prolonged cold ischemia time in kidney transplant
Exogenous toxins	Aminoglycosides, cisplatin, contrast agents, cyclosporine, tacrolimus, angiotensin-converting enzyme inhibitors, nonsteroidal antiinflammatory drugs
Endogenous toxins	Hemoglobin (hemolysis, extracorporeal circulation), myoglobin (crush injuries, seizures, influenza)
Primary kidney disease	Hemolytic uremic syndrome, crescentic glomerulonephritis

DIAGNOSIS

The diagnosis of ATN is aided by laboratory findings and radiologic investigations. A freshly voided urine is typically positive for blood and protein, and microscopy reveals red blood cells and broad, muddy-brown granular casts. Heme-positive urine in the absence of red blood cells in the sediment should raise the suspicion for hemolysis or rhabdomyolysis. In ATN, the impaired kidney reabsorptive and concentrating capacity typically results in a low urine specific gravity and a high urinary sodium and fractional excretion of sodium. The hallmark of ATN is a progressive increase in the serum creatinine and BUN. Urine biomarkers, such as neutrophil gelatinase associated lipocalm (NGAL) and cystatin C, usually increase before creatinine levels and are helpful in predicting acute tubular injury. A mild to moderate anemia is common due to dilution and decreased erythropoiesis. A high anion gap metabolic acidosis results from impaired renal excretion of acids and decreased tubular reabsorption of bicarbonate. Several electrolyte disturbances may be encountered, including hyponatremia (usually dilutional), hyperkalemia, hyperphosphatemia, hypocalcemia, and hypomagnesemia. If rhabdomyolysis is suspected, the diagnosis can be confirmed by the detection of urine myoglobin and elevated levels of serum creatine kinase. The diagnosis of nephrotoxicity may be aided by the determination of serum drug levels. Renal ultrasonography in ATN typically reveals enlarged echogenic kidneys. Prolonged severe ATN results in renal cortical necrosis and a reduction in kidney size.

TREATMENT AND PROGNOSIS

See Chapter 572.1

Treatment of ATN starts with ameliorating the kidney ischemia by restoring and maintaining the intravascular volume with IV hydration. In addition, it is important to treat the underlying cause, including with appropriate medical management of shock, sepsis, or cardiac disease. Cessation of any potential nephrotoxic agent (including NSAIDs) is critical. Dosages of all medications should be chosen based on the estimated GFR. Children with oliguria and volume overload may require fluid restriction and the judicious use of furosemide. Although furosemide can convert the clinical picture from an oliguric to a nonoliguric one (which can facilitate medical management), there is little evidence that it changes the clinical course of ATN. Children with established ATN may not respond to furosemide and are at higher risk for ototoxicity. Common indications for dialysis in ATN include fluid overload that is unresponsive to diuretics or is a hindrance to the provision of adequate nutrition, hyperkalemia unresponsive to medical management, symptomatic acid-base imbalances, and refractory hypertension.

In the absence of multiorgan failure, most children with ATN eventually regain renal function to a large extent. In the context of severe multiorgan dysfunction, renal recovery is limited, and morbidity and mortality rates remain high. Patients who recover from severe ATN remain at risk for subsequently developing chronic kidney disease.

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Chapter 562

Vascular Diseases Associated with Hematuria

562.1 Vascular Abnormalities

Prasad Devarajan

Hemangiomas, hemangiolymphangiomas, angiomyomas, and arteriovenous malformations of the kidneys and lower urinary tract are rare causes of hematuria. They can present clinically with microscopic hematuria or gross hematuria with clots. When associated cutaneous vascular malformations are present, they can offer a clue to these underlying causes of hematuria. **Angiomyolipomas,** the most common benign solid tumors of the kidney, are composed of vascular, smooth muscle, and fatty tissue elements. They can rupture on occasion to cause severe hemorrhage. Angiomyolipomas are an important component of the **tuberous sclerosis complex** (see Chapter 636.2), which includes developmental delay, facial angiofibromas, and lung cysts. Renal colic can develop with any upper tract vascular abnormality that obstructs urinary drainage, induces an inflammatory response, or distends the renal capsule. The diagnosis may be confirmed by angiography or endoscopy.

Unilateral bleeding of varicose veins of the left ureter, resulting from compression of the left renal vein between the aorta and superior mesenteric artery (mesoaortic compression), is referred to as the **nutcracker syndrome.** Patients with this syndrome typically present with persistent microscopic hematuria (and, occasionally, recurrent gross hematuria) that may be accompanied by proteinuria, left lower abdominal pain, left flank pain, or orthostatic hypotension. The diagnosis requires a high degree of suspicion and is confirmed by Doppler ultrasonography, CT scanning, phlebography of the left renal vein, or MRI.

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562.2 Renal Vein Thrombosis

Prasad Devarajan

EPIDEMIOLOGY

Renal vein thrombosis (RVT) occurs in two distinct clinical settings: (1) In newborns and infants, RVT is commonly associated with asphyxia, dehydration, shock, sepsis, congenital hypercoagulable states, central venous catheters, and maternal diabetes or preeclampsia. (2) In older children, RVT is seen in patients with nephrotic syndrome, cyanotic heart disease, inherited hypercoagulable states, sepsis, sickle cell nephropathy, Behcet syndrome, antiphospholipid syndrome following kidney transplantation, and following exposure to angiographic contrast agents.

PATHOGENESIS

RVT begins in the intrarenal venous circulation and can then extend to the main renal vein and even the inferior vena cava. Thrombus formation is mediated by endothelial cell injury resulting from hypoxia, endotoxin, or contrast media. Other contributing factors include hypercoagulability from either nephrotic syndrome or pathogenic variants in genes that encode clotting factors (e.g., deficiencies of protein C, protein S, antithrombin, and factor V Leiden); hypovolemia and decreased venous blood flow associated with septic shock, dehydration, or nephrotic syndrome; and intravascular sludging caused by polycythemia.

CLINICAL MANIFESTATIONS

The development of RVT is classically heralded by the sudden onset of gross hematuria and unilateral or bilateral flank masses. However, patients can also present with any combination of microscopic hematuria, flank pain, hypertension, or a microangiopathic hemolytic anemia with thrombocytopenia or oliguria. RVT is usually unilateral. Bilateral RVT results in acute kidney injury.

DIAGNOSIS

The diagnosis of RVT is suggested by the development of hematuria and flank masses in patients seen in the high-risk clinical settings or with the predisposing clinical features noted previously. Ultrasonography shows marked renal enlargement, and radionuclide studies reveal little or no renal function in the affected kidney(s). Doppler flow studies of the inferior vena cava and renal vein are essential to confirm the diagnosis. Contrast studies should be avoided to minimize the risk of further vascular damage.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of RVT includes other causes of hematuria that are associated with rapid development of microangiopathic hemolytic anemia or enlargement of the kidney(s). These include hemolytic uremic syndrome, hydronephrosis, polycystic kidney disease, Wilms tumor, and intrarenal abscess or hematoma. All patients with RVT should be evaluated for congenital and acquired hypercoagulable states.

TREATMENT

The primary treatment of RVT starts with aggressive supportive intensive care, including correction of fluid and electrolyte imbalance and treatment of renal insufficiency. Recommendations include additional initial treatment of bilateral RVT with tissue plasminogen activator and unfractionated heparin followed by continued anticoagulation with unfractionated or low molecular weight heparin. Treatment recommendations for unilateral RVT with inferior vena cava extension include either unfractionated or low molecular weight heparin. There is no consensus as to whether unilateral RVT without extension should be managed with heparin or with supportive therapy alone. Aggressive treatment with thrombolytic agents in all these clinical settings, as well as antithrombotic prevention of patients with documented thrombotic risk, remains controversial despite such recommendations given the significant risks of bleeding. Evidence-based data, particularly in children, do not exist despite such best practice recommendations. Children with severe hypertension secondary to RVT who are refractory to antihypertensive medications may require nephrectomy.

PROGNOSIS

Perinatal mortality rates from RVT have decreased significantly over the past 20 years. Partial or complete renal atrophy is a common sequela of RVT in the neonate, leading to an increased risk of chronic kidney disease, renal tubular dysfunction, and systemic hypertension. These complications are also seen in older children. However, recovery of kidney function is not uncommon in older children with RVT resulting from nephrotic syndrome or cyanotic heart disease with correction of the underlying etiology. Long-term follow-up of infants and children with RVT by pediatric nephrologists is recommended for the monitoring of kidney function and the early detection of hypertension and chronic kidney disease

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562.3 Sickle Cell Nephropathy

Prasad Devarajan

Gross or microscopic hematuria may be seen in children with sickle cell disease or sickle trait. Hematuria tends to resolve spontaneously in most children. Clinically apparent kidney involvement occurs more commonly in patients with sickle cell disease than in those with sickle

cell trait with the exception of an association with **renal cell carcinoma**, which is more common in patients with sickle cell trait.

ETIOLOGY

The kidney manifestations of sickle cell nephropathy (SCN) are generally related to microthrombosis secondary to sickling in the relatively hypoxic, acidic, hypertonic kidney medulla, where vascular stasis is normally present. Analgesic use, volume depletion with consequent prerenal acute kidney injury, infection, and iron-related hepatic disease are independent contributing factors. Glomerular hyperfiltration, mediated by the intrarenal production of prostaglandins and synthesis of nitric oxide, is involved in the pathogenesis of proteinuria and kidney injury in SCN.

PATHOLOGY

Ischemia, papillary necrosis, and interstitial fibrosis are common pathologic findings in SCN. The specific sickle cell glomerular lesion consists of glomerular hypertrophy, with glomerulomegaly and distended capillaries. In addition, a variety of glomerular lesions are also found in SCN; most commonly these include focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and thrombotic microangiopathy. The pathophysiology of these specific glomerulonephritic lesions in SCN is poorly understood.

CLINICAL MANIFESTATIONS

Clinical manifestations of SCN include polyuria caused by a urinary concentrating defect, renal tubular acidosis, and proteinuria associated with the glomerular lesions noted previously.

Approximately 20–30% of patients with sickle cell disease develop proteinuria. Nephrotic-range proteinuria with or without clinically apparent nephrotic syndrome occurs in up to 30% of patients with SCN, and when present, generally heralds progressive kidney disease.

TREATMENT

Tubular manifestations have no specific treatment other than those recommended generally for patients with sickle cell disease. However, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor inhibitors can be used to reduce the urine protein excretion in patients with daily amounts exceeding 500 mg and may slow the progression of chronic kidney disease. Gross hematuria secondary to papillary necrosis may respond to treatment with ε-aminocaproic acid or desmopressin acetate. Hydroxyurea and newer treatments for sickle cell disease (see Chapter 511.1) have decreased the manifestations of SCN in proportion to the other complications of the primary hemoglobinopathy.

PROGNOSIS

SCN can eventually lead to hypertension, chronic kidney disease, and progressive kidney failure. Dialysis and eventual kidney transplantation are successful treatment modalities when kidney failure is irreversible.

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562.4 Idiopathic Hypercalciuria

Prasad Devarajan

Idiopathic hypercalciuria, which may be inherited as an autosomal dominant disorder, can clinically present as recurrent *gross* hematuria, persistent microscopic hematuria, dysuria, crystalluria, or abdominal pain with or without **kidney stone** formation. Hypercalciuria can also accompany conditions resulting in hypercalcemia, such as hyperparathyroidism (see Chapter 613), vitamin D intoxication, immobilization, and sarcoidosis (see Chapter 209). Hypercalciuria may be associated with Cushing syndrome (see Chapter 619), corticosteroid therapy, tubular dysfunction secondary to Fanconi syndrome as occurs with Wilson disease (see Chapter 405.2), oculocerebrorenal (Lowe) syndrome, William syndrome, distal renal tubular acidosis, or Bartter syndrome (see Chapter 571.1). Hypercalciuria may also be seen in patients with Dent disease, which is an X-linked form of nephrolithiasis associated with hypophosphatemic rickets. Although microcrystal formation with consequent tissue irritation is believed to mediate symptoms, the precise mechanism by which hypercalciuria causes hematuria or dysuria is unknown.

DIAGNOSIS

Hypercalciuria is diagnosed by a 24-hour urinary calcium excretion >4 mg/kg. A screening test for hypercalciuria may be performed on a random urine specimen by measuring the calcium and creatinine concentrations. A spot urine calcium:creatinine ratio (mg/dL:mg/dL) >0.2 suggests hypercalciuria in an older child. Normal ratios may be as high as 0.8 in infants <7 months of age.

TREATMENT

Left untreated, hypercalciuria leads to nephrolithiasis in approximately 15% of cases. Hypercalciuria has also been associated with an increased risk for development of low bone mineral density, as well as an increased incidence of urinary tract infections. Idiopathic hypercalciuria has been identified as a risk factor in 40% of children with kidney stones, and a low urinary citrate level has been associated as a risk factor in approximately 38% of this group. Oral thiazide diuretics can normalize urinary calcium excretion by stimulating calcium reabsorption in the proximal and distal tubules. Such therapy can lead to the resolution of gross hematuria or dysuria and can prevent nephrolithiasis. The precise indications for thiazide treatment (including its duration if initiated) remain controversial.

In patients with persistent gross hematuria or dysuria, therapy is initiated with hydrochlorothiazide at a dose of 1-2 mg/kg/24 hours as a single morning dose. The dose is titrated upward until the 24-hour urinary calcium excretion is <4 mg/kg and clinical manifestations resolve. After 1 year of treatment, hydrochlorothiazide is usually discontinued, but it may be resumed if gross hematuria, nephrolithiasis, or dysuria recurs. During hydrochlorothiazide therapy, the serum potassium level should be monitored periodically to avoid hypokalemia. Potassium citrate at a dose of 1 mEq/kg/24 hours may also be beneficial, particularly in patients with low urinary citrate excretion, a low urine pH, and symptomatic dysuria or crystalluria.

Sodium restriction is important because urinary calcium excretion parallels sodium excretion. Importantly, *dietary calcium restriction is not recommended* (except in children with a massive calcium intake >250% of the recommended dietary allowance by dietary history) because calcium is a critical requirement for growth, and no evidence supports a relationship between decreased calcium intake and decreased urinary calcium levels. This is particularly important given the association of hypercalciuria in some patients with reduced bone mineral density. A number of uncontrolled, small-scale studies support a role for bisphosphonate therapy, which leads to a reduction in urinary calcium excretion and improvement in bone mineral density. Controlled studies are necessary to establish a clear role for such therapy in children with hypercalciuria.

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562.5 Nephrocalcinosis

See Chapter 584.

Chapter 563

Anatomic Abnormalities Associated with Hematuria

563.1 Congenital Anomalies

Prasad Devarajan

Gross or microscopic hematuria may be associated with many different types of malformations of the urinary tract. The sudden onset of gross hematuria after minor trauma to the flank is often associated with ureteropelvic junction obstruction, cystic kidneys, or enlarged kidneys from any cause (see Chapter 577).

563.2 Autosomal Recessive Polycystic Kidney Disease

Prasad Devarajan

Autosomal recessive polycystic kidney disease (ARPKD) (also known as ARPKD-congenital hepatic fibrosis [CHF]) is an autosomal recessive disorder occurring with an incidence of 1:20,000 and a gene carrier rate in the general population of 1/70. The gene for ARPKD ***(PKHD1** [polycystic kidney and hepatic disease 1])* encodes **fibrocystin**, a large protein (>4,000 amino acids) with multiple isoforms.

PATHOLOGY

Both kidneys are markedly enlarged and grossly show innumerable small cysts throughout the cortex and medulla. Microscopic studies demonstrate dilated, ectatic collecting ducts radiating from the medulla to the cortex. The development of progressive interstitial fibrosis and tubular atrophy during the advanced stages of the disease eventually leads to end-stage kidney disease (ESKD). ARPKD causes dual-organ disease, hence, the term *ARPKD/CHF*. Liver involvement is characterized by a basic ductal plate abnormality that leads to bile duct proliferation and ectasia, as well as progressive hepatic fibrosis.

PATHOGENESIS

Fibrocystin may form a multimeric complex with proteins of other primary genetic cystic diseases. Altered intracellular signaling from these complexes, located at epithelial apical cell surfaces, intercellular junctions, and basolateral cell surfaces in association with the focal adhesion complex, is a critical feature of the disease pathophysiology.

Over 300 pathogenic variants in *PKHD1* (without identified specific hot spots) cause disease, and the same pathogenic variant can give variable degrees of disease severity in the same family. This clinical observation is consistent with preclinical data demonstrating many environmental and unknown genetic factors affecting disease expression. The false-negative rate for genetic diagnosis is approximately 10%. Limited available information suggests only a gross genotype–phenotype correlation: pathogenic variants that modify fibrocystin appear to cause less severe disease than those that truncate fibrocystin.

CLINICAL MANIFESTATIONS

The diagnosis of ARPKD is often made antenatally by the demonstration of oligohydramnios and bilateral enlarged kidneys on prenatal ultrasound. The typical infant presents with bilateral flank masses during the neonatal period or in early infancy. ARPKD may be associated with respiratory distress and spontaneous pneumothorax in the neonatal period. Perinatal demise (25–30%) appears to be associated with truncating pathogenic variants. Severe bilateral cases often result in the **oligohydramnios complex (Potter syndrome),** which is marked by low-set ears, micrognathia, flattened nose, limb-positioning defects, intrauterine growth restriction, and pulmonary hypoplasia (see Chapter 574). Respiratory distress may also be secondary to large kidneys that compromise the diaphragm function. Hypertension is usually noted within the first few weeks of life, is often severe, and requires aggressive multidrug therapy for control. Oliguria and acute kidney injury are uncommon, but transient hyponatremia may be seen, which often responds to diuresis. Kidney function is usually impaired but may be initially normal in 20–30% of patients. Approximately 50% of patients with a neonatal-perinatal presentation develop ESKD by age 10 years.

ARPKD is increasingly recognized in infants (and, rarely, in adolescents and young adults) with a mixed renal-hepatic clinical picture. Such children and young adults often present with predominantly hepatic manifestations in combination with variable degrees of kidney disease. **Hepatic fibrosis** manifests as portal hypertension, hepatosplenomegaly, gastroesophageal varices, episodes of ascending cholangitis, prominent cutaneous periumbilical veins, reversal of portal vein flow, and thrombocytopenia. CHF may manifest with cholangiodysplastic changes or a frank **Caroli type** with marked intrahepatic bile duct dilation, affecting the whole liver or just one segment; biliary tract disease increases the risk of ascending cholangitis. Kidney findings in patients with a hepatic presentation may range from asymptomatic abnormal renal ultrasonography to systemic hypertension and chronic kidney disease. In the newborn, clinical evidence of liver disease by radiologic or clinical laboratory assessment is present in approximately 50% of children and believed to be universal by microscopic evaluation. Natural history studies of ARPKD patients presenting as infants and young children have classified this group in terms of the severity of their dual-organ phenotype: 40% have the severe kidney/severe liver phenotype, and 20% each have the severe kidney/mild liver, severe liver/mild kidney, and mild kidney/mild liver phenotype.

DIAGNOSIS

The diagnosis of ARPKD is strongly suggested by bilateral palpable flank masses in an infant with pulmonary hypoplasia, oligohydramnios, hypertension, and the absence of renal cysts by sonography of the parents (Fig. 563.1). Markedly enlarged and uniformly hyperechogenic kidneys with poor corticomedullary differentiation are commonly seen on ultrasonography (Fig. 563.2). The diagnosis is supported by clinical and laboratory signs of hepatic fibrosis, pathologic findings of ductal plate abnormalities seen on liver biopsy, anatomic and pathologic proof of ARPKD in a sibling, or parental consanguinity. The diagnosis can be confirmed by genetic testing. The differential diagnosis includes other causes of bilateral renal enlargement and/or cysts, such as multicystic dysplasia, hydronephrosis, Wilms tumor, and bilateral renal vein thrombosis (Tables 563.1 and 563.2).

Nephronophthisis, an autosomal recessive disorder with kidney fibrosis, tubular atrophy, and cyst formation, is a common cause of ESKD in children and adolescents (see Tables 563.1 and 563.2) (see also Chapter 561). Associated external findings include retinal degeneration (Senior-Løken syndrome), cerebellar ataxia (Joubert syndrome), and hepatic fibrosis (Boichis disease). Symptoms include polyuria (salt wasting, poor concentrating ability), failure to thrive, and anemia. Hypertension and edema are seen later when ESKD develops. Prenatal diagnostic testing using genetic linkage analysis or direct pathogenic variant analysis is available in families with a previously affected child.

Preimplantation genetic diagnosis with in vitro fertilization is available for families with a child affected with ARPKD.

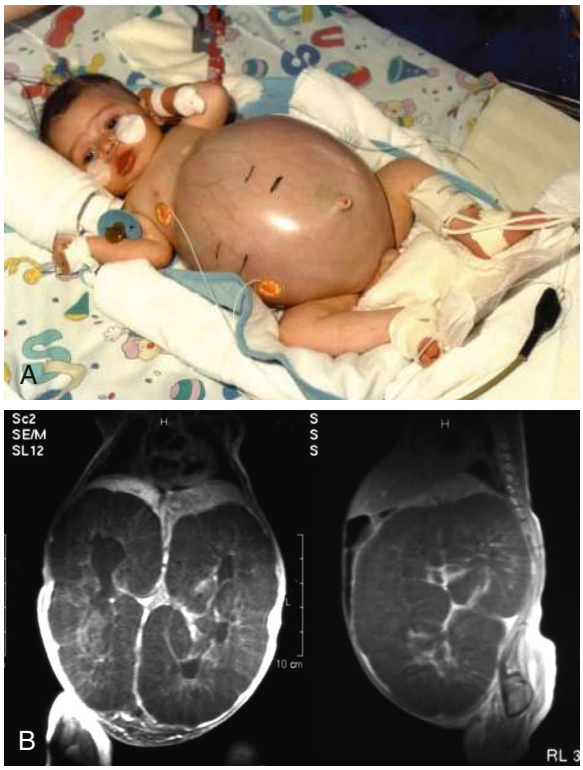

Fig. 563.1 A, Severe nephromegaly in a 3-mo-old infant with autosomal recessive polycystic kidney disease, with x-rays (B). *(From Bakkaloglu SA, Schaefer F. Disease of the kidney and urinary tract in children. In: Skorecki K, Chertow GM, Marsden PA, et al., eds. Brenner & Rector's The Kidney. 10th ed. Philadelphia: Elsevier; 2016: Fig. 74-6, p. 2320.)*

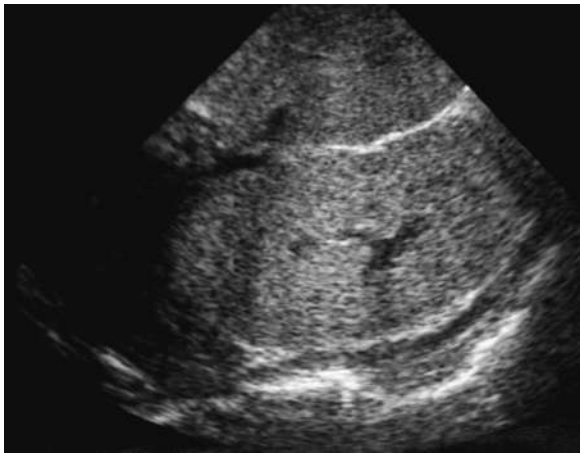

Fig. 563.2 Ultrasound examination of a neonate with autosomal recessive polycystic kidney disease demonstrating renal enlargement (9 cm) and increased diffuse echogenicity with complete loss of corticomedullary differentiation resulting from multiple small cystic interfaces.

TREATMENT

The treatment of ARPKD is supportive. Aggressive ventilatory support is often necessary in the neonatal period secondary to pulmonary hypoplasia, hypoventilation, and the respiratory illnesses of prematurity. Careful management of hypertension (angiotensin-converting enzyme inhibitors, and other antihypertensive medications as needed), fluid and electrolyte abnormalities, osteopenia, and clinical manifestations of kidney insufficiency are essential. Children with severe respiratory failure or feeding intolerance from enlarged kidneys can require unilateral or, more commonly, bilateral nephrectomies, prompting the need for renal replacement therapy. For many children approaching ESKD therapy, significant portal hypertension is present. This in combination with the dramatic improvement in liver transplantation survival has led to consideration of dual kidney and liver transplantation in a carefully selected group of patients. Dual transplantation thus avoids the later development of end-stage liver disease despite successful kidney transplantation.

PROGNOSIS

Mortality rates have improved dramatically, although approximately 30% of patients die in the neonatal period from complications of pulmonary hypoplasia. Neonatal respiratory support and renal replacement therapies have increased the 10-year survival of children surviving beyond the first year of life to >80%. The 15-year survival rate is currently estimated at 70–80%. Consideration of dual kidney and liver transplantation and the development of disease-specific therapies for pediatric clinical trials will further positively impact the natural history of ARPKD. An important resource for families of patients is the ARPKD/CHF Alliance (www.arpkdchf.org).

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563.3 Autosomal Dominant Polycystic Kidney Disease

Prasad Devarajan

Autosomal dominant polycystic kidney disease (ADPKD), also known as adult-onset polycystic kidney disease, is the most common hereditary human kidney disease, with an incidence of 1/400 to 1/1,000. It is a systemic disorder with possible cyst formation in multiple organs (liver, pancreas, spleen, brain) and the possible development of saccular cerebral aneurysms.

PATHOLOGY

Both kidneys are enlarged and show large cortical and medullary cysts originating from all regions of the nephron.

PATHOGENESIS

Approximately 85% of patients with ADPKD have pathogenic variants that map to the *PKD1* gene on the short arm of chromosome 16, which encodes polycystin, a transmembrane glycoprotein. Another 10–15% of ADPKD pathogenic variants map to the *PKD2* gene on the long arm of chromosome 4, which encodes polycystin 2, a proposed nonselective cation channel. The majority of pathogenic variants appear to be unique to a given family. At present, a pathogenic variant can be found in 85% of patients with well-characterized disease.

Approximately 8–10% of patients will have de novo, disease-causing pathogenic variants. Pathogenic variants of *PKD1* are associated with more severe renal disease than pathogenic variants of *PKD2*. The pathophysiology of the disease appears to be related to the disruption of normal multimeric cystoprotein complexes, with consequent abnormal intracellular signaling resulting in abnormal proliferation, tubular secretion, and cyst formation. Abnormal growth factor expression, coupled with low intracellular calcium and elevated cyclic adenosine monophosphate, appear to be important features leading to formation of cysts and progressive enlargement. Pathogenic variants in *GANAB* have been reported in *PKD1*- and *PKD2*-negative patients.

CLINICAL PRESENTATION

The severity of renal disease and the clinical manifestations of ADPKD are highly variable. Symptomatic ADPKD most commonly occurs in the fourth or fifth decade of life. However, symptoms, including gross

Table 563.1 Differential Diagnosis in ARPKD and ADPKD Genotypes

	ASSOCIATED DISEASE	RENAL PHENOTYPE	EXTRARENAL PHENOTYPE
CLASSIC ARPKD			
	PKHD1, possibly *DZIP1L*	Bilateral nephromegaly, heterogenous parenchymal echogenicity with salt and pepper pattern Prenatal onset: bilateral nephromegaly, oligohydramnios, Potter-like syndrome	Progressive hepatic fibrosis, Caroli syndrome, portal hypertension
CLASSIC ADPKD			
PKD1	ADPKD-*PKD1* with truncating variant	Innumerable bilateral kidney cysts causing progressive kidney enlargement and reduction in eGFR; median age at ESKD about 55 years	Polycystic liver disease, mild to severe, SAH-CNS aneurysms*
PKD1	ADPKD-*PKD1* with nontruncating variant	Innumerable bilateral kidney cysts causing progressive kidney enlargement and reduction in eGFR; median age at ESKD about 67 years	Polycystic liver disease, mild to severe, SAH-CNS aneurysms*
PKD2	ADPKD-*PKD2*	Innumerable bilateral kidney cysts causing progressive kidney enlargement and reduction in eGFR; median age at ESKD about 79 years	Polycystic liver disease, mild to severe, SAH-CNS aneurysms*
ADPKD-LIKE PHENOTYPE			
GANAB	ADPKD-*GANAB*	Bilateral renal cysts, preserved kidney function	Polycystic liver disease, mild to severe
DNAJB11	ADPKD-*DNAJB11*	Normal or small-sized kidneys with multiple small renal cysts; possible evolution to ESKD after 60 years	Polycystic liver disease, absent to moderate
ADTKD-ASSOCIATED GENES			
HNF1B	ADTKD-*HNF1B*	Bilateral renal cysts in about 45% of affected individuals, occasionally mimics ADPKD imaging presentation; evolution to ESKD is highly variable, from childhood-onset ESKD to preserved kidney function throughout life	Diabetes, gout, hyperuricemia, hypomagnesaemia, elevated liver enzymes, bicornate uterus, solitary kidney
MUC1	ADTKD-*MUC1*	Normal or small-sized kidneys, few small renal cysts in half of patients; evolution to ESKD highly variable, age 20-70 years	Gout
SEC61A1	ADTKD-*SEC61A1*	Normal or small-sized kidneys, bilateral small renal cysts in about 50% of individuals	Congenital anemia, intrauterine growth retardation, neutropenia
UMOD	ADTKD-*UMOD*	Normal or small-sized kidneys, few small renal cysts in a third of patients, unilateral or bilateral; evolution to ESKD highly variable, age 20-70 years	Gout
ADPLD-ASSOCIATED GENES			
PRKCSH	ADPLD	Few renal cysts occasionally reported	Polycystic liver disease, mild to severe
SEC63	ADPLD	Few renal cysts occasionally reported	Polycystic liver disease, mild to severe
ALG8	ADPLD	Few renal cysts occasionally reported	Polycystic liver disease, mild to moderate
SEC61B	ADPLD	No renal cysts observed to date in the two families reported with a pathogenic variant in this gene	Polycystic liver disease, mild to moderate
LRP5	ADPLD	Few renal cysts occasionally reported	Polycystic liver disease, mild to moderate
RECESSIVE INHERITANCE			
PKHD1	ARPKD	Antenatally enlarged hyperechogenic kidneys; multiple bilateral millimeter-sized cysts; ESKD in the first decade of life in about 50% of individuals but milder renal presentation with diagnosis in adulthood possible	Congenital hepatic fibrosis, Caroli syndrome, small liver cysts in heterozygous patients
DZIP1L	ARPKD	Antenatal enlarged hyperechogenic kidneys; multiple bilateral millimeter-sized cysts; progression to ESKD variable (second and third decade of life)	No obvious extrarenal manifestations reported in the seven patients identified to date

Continued

Table 563.1 Differential Diagnosis in ARPKD and ADPKD Genotypes—cont'd

	ASSOCIATED DISEASE	RENAL PHENOTYPE	EXTRARENAL PHENOTYPE
PMM2	Hyperinsulinemic hypoglycemia with PKD	Antenatal enlarged hyperechogenic kidneys, enlarged kidneys with multiple cysts; progression to ESKD variable, from infancy to early adulthood	Hyperinsulinemic hypoglycemia; small liver cysts in some patients
SYNDROMIC FORMS OF PKD			
TSC1 or *TSC2*	Tuberous sclerosis	Multiple and bilateral angiomyolipomas and renal cysts; kidney function usually preserved; possible evolution to ESKD, either by destruction of the renal parenchyma by multiple angiomyolipomas or following nephrectomies for hemorrhagic angiomyolipomas; if there is contiguous gene deletion of *TSC2* and *PKD1*, severe PKD with evolution to ESKD occurs before age 30 years	CNS (cortical tubers, astrocytomas, epilepsy, and intellectual disabilities); skin lesions (facial angiofibromas and hypopigmented spots); pulmonary lymphangioleiomyomatosis; cardiac rhabdomyoma and retinal hamartoma; polycystic liver disease if contiguous deletion of both *PKD1* and *TSC2*
VHL	Von Hippel-Lindau disease	Bilateral renal cysts, renal cell carcinoma	Hemangioblastomas of the retina, spine, or brain; pheochromocytoma; neuroendocrine tumor of the pancreas
COL4A1	HANAC syndrome or *COL4A1*-related disease	Bilateral renal cysts occasionally reported; patients can develop renal insufficiency after about age 50-60 years	Microscopic hematuria, aneurysms, muscle cramps, elevated creatine phosphokinase, tortuosity of the retinal arteries
OFD1	Oro-facial-digital syndrome type 1	X-linked, embryonically lethal in males, PKD in females	Cleft palate, facial dysmorphy; syndactyly, clinodactyly, or polydactyly; intellectual disabilities; polycystic liver disease

*Intracranial aneurysms in 9–12% of patients with ADPKD.
ADPKD, Autosomal dominant PKD; ADPLD, autosomal dominant polycystic liver disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CNS, central nervous system; eGFR, estimate glomerular filtration rate; ESKD, end-stage kidney disease; HANAC, hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; PKD, polycystic kidney disease; SAH, subarachnoid hemorrhage.
From Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet*. 2019;393:919–932. Table 1.

Table 563.2 Autosomal Recessive Polycystic Kidney Disease and Hepatorenal Fibrocystic Disease Phenocopies

DISEASE	GENE(S)	RENAL DISEASE	HEPATIC DISEASE	SYSTEMIC FEATURES
ARPKD	*PKHD1*	Collecting duct dilation	CHF; Caroli disease	No
ADPKD	*PKD1; PKD2*	Cysts along entire nephron	Biliary cysts; CHF (rare)	Yes: adults
NPHP	*NPHP1-NPHP16*	Cysts at the corticomedullary junction	CHF	+/–
Joubert syndrome and related disorders	*JBTS1-JBTS20*	Cystic dysplasia; NPHP	CHF; Caroli disease	Yes
Bardet-Biedl syndrome	*BBS1-BBS18*	Cystic dysplasia; NPHP	CHF	Yes
Meckel-Gruber syndrome	*MKS1-MKS10*	Cystic dysplasia	CHF	Yes
Oral-facial-digital syndrome, type I	*OFD1*	Glomerular cysts	CHF (rare)	Yes
Glomerulocystic disease	*PKD1; HNF1B; UMOD*	Enlarged; normal or hypoplastic kidneys	CHF (with PKD1 pathogenic variants)	+/–
Jeune syndrome (asphyxiating thoracic dystrophy)	*IFT80 (ATD2) DYNC2H1 (ADT3) ADT1, ADT4, ADT5*	Cystic dysplasia	CHF; Caroli disease	Yes
Renal-hepatic-pancreatic dysplasia (Ivemark II)	*NPHP3, NEK8*	Cystic dysplasia	Intrahepatic biliary dysgenesis	Yes
Zellweger syndrome	*PEX1-3;5-6;10-11;13;14;16;19;26*	Renal cortical microcysts	Intrahepatic biliary dysgenesis	Yes

ADPKD, Autosomal dominant PKD; ARPKD, autosomal recessive polycystic kidney disease; CHF, congenital hepatic fibrosis; NPHP, nephronophthisis.
Modified from Guay-Woodford LM, Bissler JJ, Braun MC, et al. Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: report of an international conference. *J Pediatr*. 2014;165:611–617.

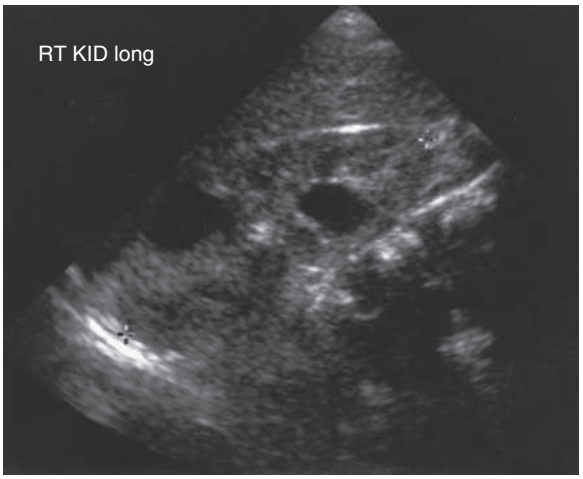

Fig. 563.3 Ultrasound examination of an 18-mo-old male with autosomal dominant polycystic kidney disease demonstrating renal enlargement (10 cm) and two large cysts.

or microscopic hematuria, bilateral flank pain, abdominal masses, hypertension, and urinary tract infection, may be seen in neonates, children, and adolescents. With the increased utilization of abdominal sonography in the pediatric population, as well as ADPKD families requesting possible screening in their asymptomatic, at-risk offspring, most children with ADPKD are diagnosed by abnormal renal sonography in the absence of symptoms. Renal ultrasonography usually demonstrates multiple bilateral macrocysts in enlarged kidneys (Fig. 563.3), although normal kidney size and unilateral disease may be seen in the early phase of the disease in children.

ADPKD is a multiorgan disorder affecting many tissue types. Cysts may be asymptomatic but present within the liver, pancreas, spleen, and ovaries and, when present, help confirm the diagnosis in childhood. **Intracranial aneurysms,** which appear to segregate within certain families, have an overall prevalence of 15% and are an important cause of mortality in adults but only occasionally occur in children. Mitral valve prolapse is seen in approximately 12% of children; aortic and coronary artery aneurysms and aortic valve insufficiency are noted in affected adults. Hernias, bronchiectasis, and intestinal diverticula can also occur in these children.

DIAGNOSIS

ADPKD is confirmed by the presence of enlarged kidneys with bilateral macrocysts in a patient with an affected first-degree relative. De novo pathogenic variants occur in 8–10% of patients with newly diagnosed disease. The diagnosis might be made in children before their affected parent, making parental renal sonography an important diagnostic test to be performed in families with no apparent family history. Among patients with genetically defined ADPKD, screening renal ultrasonography results may be normal in ≤20% by 20 years of age and <5% by 30 years of age.

Prenatal diagnosis is suggested from the presence of enlarged kidneys with or without cysts on ultrasonography in families with known ADPKD. Prenatal DNA testing is available in families with affected members whose disease is caused by identified pathogenic variants in the *PKD1* or *PKD2* genes.

The differential diagnosis includes renal cysts associated with glomerulocystic kidney disease, tuberous sclerosis, and von Hippel-Lindau disease, which may be inherited in an autosomal dominant pattern (see Table 563.1). The neonatal manifestations of ADPKD and ARPKD may rarely be indistinguishable.

TREATMENT AND PROGNOSIS

Treatment of ADPKD is primarily supportive. Control of blood pressure is critical because the rate of disease progression in ADPKD correlates with the presence of hypertension. Angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists are agents of choice. Obesity, dietary salt and protein excess, caffeine ingestion, smoking, multiple pregnancies, and male gender appear to accelerate the disease progression. Older patients with a family history of intracranial aneurysm rupture should be screened for cerebral aneurysms. Although the approach remains controversial, most nephrologists now recommend initial screening for cerebral aneurysms with an MR angiogram around 18 years of age in asymptomatic patients with a family history of ADPKD and associated aneurysms.

Although neonatal ADPKD may be fatal, long-term survival of the patient and the kidneys is possible for children surviving the neonatal period. ADPKD that occurs initially in older children has a favorable prognosis, with normal kidney function during childhood seen in >80% of children. Pain may be a manifestation of infection, hemorrhage, cyst rupture, stones, or tumors and should be managed appropriately with pain medications and specifically based on its etiology.

Although disease-specific therapy is not yet available, clinical trials are in progress based on promising preclinical laboratory investigations. These potential therapies include renin-angiotensin blockade, vasopressin V_2 receptor antagonism (tolvaptan), statins (to reduce pain), and somatostatin analogues. Tolvaptan has been effective in adults in slowing the progression of renal impairment. A valuable resource for patients and their families is the Polycystic Kidney Disease Foundation (www.pkdcure.org).

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563.4 Trauma

Prasad Devarajan

Infants and children are more susceptible to kidney injury following blunt or penetrating injury to the back or abdomen because of their decreased muscle mass "protecting" the kidney. Gross or microscopic hematuria, flank pain, and abdominal rigidity can occur; associated injuries may be present (see Chapter 80). In the absence of hemodynamic instability, most kidney trauma can be managed nonoperatively. Urethral trauma can result from crush injury, often associated with a fractured pelvis or from direct injury. Such injury is suspected in the appropriate clinical setting when gross blood appears at the external urethral meatus. Rhabdomyolysis and consequent acute kidney injury is another complication of crush injury that can be ameliorated by vigorous fluid resuscitation. There may be a relationship between microscopic hematuria and recreational accidents in individuals >16 years of age, none of whom exhibited hypotension or required surgical intervention.

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563.5 Renal Tumors

See Chapters 547 and 548.

Chapter 564

Lower Urinary Tract Causes of Hematuria

564.1 Infectious Causes of Cystitis and Urethritis

Prasad Devarajan

Gross or microscopic hematuria may be associated with bacterial, mycobacterial, or viral infections of the bladder (see Chapter 575).

564.2 Hemorrhagic Cystitis

Prasad Devarajan

Hemorrhagic cystitis is defined as the presence of sustained hematuria and lower urinary tract symptoms (e.g., dysuria, frequency, urgency) in the absence of other bleeding conditions such as vaginal bleeding, a generalized bleeding condition, or a bacterial urinary tract infection. Depending on the severity, patients can present with microscopic or gross hematuria, often with clots. In severe forms, bleeding can lead to a significant decrease in blood hemoglobin levels and symptoms of lower urinary tract obstruction.

Hemorrhagic cystitis can occur in response to chemical toxins (cyclophosphamide, penicillins, busulfan, thiotepa, dyes, insecticides), viruses (adenovirus types 11 and 21 [see Chapter 309] and influenza A [see Chapter 305]), radiation, and amyloidosis. The polyoma **BK virus** (see Chapter 321), present latently in immunocompetent hosts, is associated with the development of drug-induced cystitis in immunosuppressed patients. The pediatric bone marrow transplantation population is particularly susceptible to hemorrhagic cystitis.

For chemical irritation related to the use of cyclophosphamide, hydration, bladder washes, and the use of mesna disulfide, which inactivates urinary cyclophosphamide metabolites, helps to protect the bladder. Administration of oral cyclophosphamide in the morning followed by aggressive oral hydration throughout the remainder of the day is very effective in minimizing the risk of hemorrhagic cystitis. Treatment of hemorrhagic cystitis consists of a combination of intensive intravenous hydration, forced diuresis, analgesia, and spasmolytic drugs. Consultation with a urologist is recommended for more invasive measures if the cystitis does not respond to conservative measures. Gross hematuria associated with viral hemorrhagic cystitis usually resolves within 1 week.

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564.3 Vigorous Exercise

Prasad Devarajan

Gross or microscopic hematuria can follow vigorous exercise. **Exercise-induced hematuria** is less common in females and can be associated with dysuria. Approximately 30–60% of runners completing marathons have dipstick-positive urine for blood. In limited follow-up, none appeared to have any significant kidney or urinary tract abnormalities. The color of the urine following vigorous exercise can vary from red to black. Blood clots may be rarely present in the urine. Findings on urine culture, intravenous pyelography, voiding cystourethrography, and cystoscopy are normal in most patients. This seems to be a benign condition, and the hematuria generally resolves within 48 hours after cessation of exercise. The absence of red blood cell casts or evidence of renal disease and the presence of dysuria and blood clots in some patients suggest that the source of bleeding lies in the lower urinary tract. **Rhabdomyolysis** with **myoglobinuria** or hemoglobinuria must be considered in the differential diagnosis when the condition is associated with symptoms in the appropriate clinical context. Hydronephrosis or other anatomic abnormalities must be considered in any child who presents with hematuria (particularly gross hematuria) after mild exercise or following mild trauma. Appropriate imaging studies are indicated in this setting.

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Section 3

Conditions Particularly Associated With Proteinuria

Chapter 565

Clinical Evaluation of the Child with Proteinuria

Francisco X. Flores

NORMAL PHYSIOLOGY

The charge and size selective properties of the glomerular capillary wall prevent significant amounts of albumin, globulin, and other large plasma proteins from entering the urinary space (see Chapter 557). Smaller proteins (low molecular weight proteins) do cross the capillary wall but are reabsorbed by the proximal tubule. A very small amount of protein that normally appears in the urine is the result of normal tubular secretion. The normally excreted protein mostly consists of **Tamm-Horsfall protein (uromodulin)**, a protective glycoprotein secreted by the tubules that inactivates cytokines.

PATHOPHYSIOLOGY OF PROTEINURIA

Abnormal amounts of protein may appear in the urine from three possible mechanisms: *glomerular proteinuria,* which occurs as a result of disruption of the glomerular capillary wall; *tubular proteinuria,* a tubular injury or dysfunction that leads to ineffective reabsorption of mostly low molecular weight proteins; and *increased production of plasma proteins* (in multiple myeloma, rhabdomyolysis, or hemolysis), which may cause the production or release of very large amounts of protein that are filtered at the glomerulus and overwhelm the absorptive capacity of the proximal tubule.

MEASUREMENT OF URINE PROTEIN

Urine protein can be measured in random collected samples or in timed (e.g., 24-hour or overnight) samples. Tests to accurately quantify the urine protein concentration rely on precipitation with sulfosalicylic acid and measurement of turbidity (Table 565.1).

Table 565.1 Quantification of Proteinuria in Children

METHOD	INDICATIONS	NORMAL RANGE	COMMENTS
Dipstick testing	Routine screening for proteinuria performed in the office	Negative or trace in a concentrated urine specimen (specific gravity: ≥1.020) Test interpretation: 1+ ~30 mg/dL 2+ ~100 mg/dL 3+ ~300 mg/dL	False-positive test can occur if urine is very alkaline (pH >8.0) or very concentrated (specific gravity: >1.025), or when there is pus, vaginal secretions, or semen present
24-hr urine for protein and creatinine*excretion	Quantitation of proteinuria (as well as creatinine clearances)	<150 mg/m^2/24 hr	More accurate than spot urine analysis; inconvenient for patient; the creatinine content should be measured to determine whether the specimen is truly a 24-hr collection. The amount of creatinine in a 24-hr specimen can be estimated as follows: females, 15-20 mg/kg; males, 20-25 mg/kg
Spot urine for protein/creatinine ratio, preferably on first morning urine specimen	Semiquantitative assessment of proteinuria	<0.2 mg protein/mg creatinine in children older than 2 yr old <0.5 mg protein/mg creatinine in those 6-24 mo old	Simplest method to quantitate proteinuria; less accurate than measuring 24-hr proteinuria
Microalbuminuria	Assess risk of progressive glomerulopathy in patients with diabetes mellitus	<30 mg urine albumin per gram of creatinine on first morning urine	Therapy should be intensified in diabetics with microalbuminuria

*Note that in a 24-hr urine specimen, the creatinine content should be measured to determine whether the specimen is truly a 24-hr collection. The amount of creatinine in a 24-hr specimen can be estimated as follows: females, 15-20 mg/kg and males, 20-25 mg/kg.

Adapted from Hogg RJ, Portman RJ, Milliner D, et al. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a Pediatric Nephrology Panel Established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk Assessment, Detection, and Elimination (PARADE). *Pediatrics.* 2000;105(6):1242–1249.

Urine Dipstick Measurement of Protein

The total protein concentration in urine can be estimated with chemically impregnated plastic strips that contain a pH-sensitive colorimetric indicator that changes color when negatively charged proteins, such as albumin, bind to it. Dipsticks primarily detect albuminuria and are less sensitive for other forms of proteins (low molecular weight proteins, Bence-Jones protein, gamma globulins). Visual changes in the color of the dipstick are a semiquantitative measure of urinary protein concentration. The dipstick is reported as negative, trace (10-29 mg/dL), 1+ (30-100 mg/dL), 2+ (100-300 mg/dL), 3+ (300-1,000 mg/dL), and 4+ (>1,000 mg/dL). False-positive results can occur with a very high urine pH (>7.0), a highly concentrated urine specimen, contamination of the urine with blood, and the presence of pyuria or prolonged dipstick immersion. False-negative test results can occur in patients with a low urine pH (<4.5), dilute urine or a large volume of urine output, or in disease states in which the predominant urinary protein is not albumin.

Positive urine dipstick test for protein is considered to be present if there is more than a trace (10-29 mg/dL) in a urine sample in which the specific gravity is <1.010. If the specific gravity is >1.015, the dipstick must read ≥1+ (>30 mg/dL) to be considered clinically significant.

Because the dipstick reaction offers only a qualitative measurement of urinary protein excretion, children with persistent proteinuria should have proteinuria quantitated more precisely. **Timed (24-hour) urine collections** offer more precise information regarding urine protein excretion than a randomly performed dipstick test. Urinary protein excretion in the normal child is <100 mg/m^2/day or a total of 150 mg/day. In neonates, normal urinary protein excretion is higher, up to 300 mg/m^2, because of reduced reabsorption of filtered proteins. A reasonable upper limit of normal protein excretion in healthy children is 150 mg/24 hr. More specifically, normal protein excretion in children is defined as ≤4 mg/m^2/hr, abnormal proteinuria is defined as excretion of 4-40 mg/m^2/hr, and nephrotic-range proteinuria is defined as > 40 mg/m^2/hr.

Timed urine collections are cumbersome to obtain, and the sensitivity and specificity of the test can be influenced by fluid intake, the volume of urine output, and the importance of including a complete collection without missed voids.

Urine Protein-to-Creatinine Ratio Measurement

Urine protein-to-creatinine ratio measurement of an untimed (spot) urine specimen has largely replaced timed urine collection. In children, urine protein-to-creatinine ratios have been shown to be significantly correlated with measurements of 24-hour urine protein and are useful to screen for proteinuria and to longitudinally monitor urine protein levels.

This ratio is calculated by dividing the urine protein concentration (mg/dL) by the urine creatinine concentration (mg/dL) to provide a simple measure. It should be ideally performed on a first morning voided urine specimen to eliminate the possibility of orthostatic (postural) proteinuria (see Chapter 566.2). A ratio of <0.5 in children <2 years of age and <0.2 in children >2 years of age suggests normal urinary protein excretion. A ratio >2 suggests nephrotic-range proteinuria.

CLINICAL CONSIDERATIONS

The finding of proteinuria in children and adolescents in a single, non–first morning urine specimen is common, varying between 5% and 15%. The prevalence of persistent proteinuria on repeated testing is much less common. The challenge is to differentiate the child with proteinuria related to renal disease from the otherwise healthy child with transient or other benign forms of proteinuria. When proteinuria is detected, it is important to determine whether it is transient, orthostatic, or fixed in nature.

Microalbuminuria is defined as the presence of albumin in the urine above the normal level but below the detectable range of conventional urine dipstick methods. In adults, persistent microalbuminuria (defined as a urinary albumin excretion of 30-300 mg/g creatinine on at least two to three samples) is accepted as evidence of diabetic nephropathy and also a predictor of cardiovascular and renal disease. The mean level of urinary albumin excretion falls between 8 and 10 mg/g of creatinine in children >6 years of age. Similar to adults, microalbuminuria in children has been found to be associated with obesity and to predict, with reasonable specificity, the development of diabetic nephropathy in type 1 diabetes mellitus.

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Chapter 566

Conditions Associated with Proteinuria

566.1 Transient Proteinuria

Francisco X. Flores

The majority of children found to have positive tests for protein on urinary dipsticks will have negative evaluations on repeated dipsticks and normal urinary protein if formally quantitated. Approximately 10% of children who undergo random urinalysis have proteinuria by a single dipstick measurement. Across the school-age spectrum, this finding occurs more commonly in adolescents than in younger children. In most cases, serial testing of the patient's urine demonstrates resolution of the abnormality. This phenomenon defines **transient proteinuria,** and its cause remains elusive. Defined contributing factors include a temperature >38.3°C (101°F), exercise, dehydration, cold exposure, heart failure, recent use of epinephrine, seizures, or stress. Transient proteinuria usually does not exceed 1-2+ on the dipstick. No evaluation or therapy is needed for children with this benign condition, and it resolves spontaneously or as the cause resolves. Persistence of proteinuria, even if low grade, is not consistent with the diagnosis and suggests the need for additional evaluation (Fig. 566.1).

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566.2 Orthostatic (Postural) Proteinuria

Francisco X. Flores

Orthostatic proteinuria is the most common cause of *persistent* proteinuria in school-age children and adolescents, occurring in up to 60% of children with persistent proteinuria. Children with this condition are usually asymptomatic, and the condition is discovered by routine urinalysis. Patients with orthostatic proteinuria excrete normal or minimally increased amounts of protein in the supine position. In the upright position, urinary protein excretion may be increased 10-fold, up to 1,000 mg/24 hr (1 g/24 hr). *Hematuria, hypertension, hypoalbuminemia, edema, and renal dysfunction are absent.*

In a child with persistent asymptomatic proteinuria, the initial evaluation should include an assessment for orthostatic proteinuria. It begins with the collection of a first morning urine sample, with subsequent testing of any urinary abnormalities by a complete urinalysis and determination of a spot urine protein-to-creatinine ratio (see Fig. 566.1). The correct collection of the first morning urine sample is critical. The child must fully empty the bladder before going to bed and then collect the first voided urine sample immediately upon arising in the morning. The absence of proteinuria (dipstick negative or trace for protein; and a normal ratio of urinary protein [uPr; mg/dL] to urinary creatinine [uCr; mg/dL] = [uPr/uCr] <0.2) on the first morning urine sample for 3 consecutive days confirms the diagnosis of orthostatic proteinuria. No further evaluation is necessary, and the patient and family should be reassured of the benign nature of this condition. However, if there are other abnormalities of the urinalysis (e.g., hematuria), or if the urine uPr:uCr ratio is >0.2, the patient should be referred to a pediatric nephrologist for a complete evaluation.

The cause of orthostatic proteinuria is unknown, although altered renal hemodynamics and partial left renal vein obstruction in the upright, lordotic position have been proposed as possible causes. An increased body mass index is recognized as a strong correlate of orthostatic proteinuria. Long-term follow-up studies in young adults suggest that orthostatic proteinuria is a benign process, but similar data are not available for children. Therefore long-term follow-up of children is prudent. Patients should be monitored for the development of nonorthostatic proteinuria, particularly in the presence of hematuria, hypertension, or edema. Such findings may herald underlying kidney disease.

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566.3 Fixed Proteinuria

Francisco X. Flores

Children found to have fixed proteinuria on a first morning urine sample on three separate occasions should be further investigated. Fixed proteinuria is defined as a first morning urine sample that is ≥1+ on dipstick testing with a urine specific gravity >1.015 or with a urine protein-to-creatinine ratio of ≥0.2. Fixed proteinuria indicates a potential kidney disease caused by either glomerular or tubular disorders.

GLOMERULAR PROTEINURIA

The glomerular capillary wall consists of three layers: the fenestrated capillary endothelium, the glomerular basement membrane, and the podocytes (with foot processes and intercalated slit diaphragms) (Fig. 566.2). Glomerular proteinuria results from alterations in the permeability of any of the layers of the glomerular capillary wall to normally filtered proteins and occurs in a variety of renal diseases (Table 566.1). Glomerular proteinuria can range widely from <1 g to >30 g of protein in a 24-hour period. The podocyte is the predominant cell of injury in most glomerular diseases characterized by heavy proteinuria.

Glomerular proteinuria should be suspected in any patient with a first morning urine protein-to-creatinine ratio >1.0, or significant proteinuria of any degree, accompanied by hypertension, hematuria with active urine sediment, edema, or renal dysfunction. Disorders characterized primarily by proteinuria include idiopathic (minimal change disease) nephrotic syndrome, secondary causes of nephrotic syndrome, focal segmental glomerulosclerosis, mesangial proliferative glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, diabetic nephropathy, and obesity-related glomerulopathy. Other renal disorders that can include proteinuria as a prominent feature include acute postinfectious glomerulonephritis, immunoglobulin A nephropathy, systemic lupus erythematosus nephritis, IgA vasculitis (formerly Henoch-Schönlein purpura) nephritis, and Alport syndrome.

The initial evaluation of a child with fixed proteinuria should include the measurement of serum creatinine and an electrolyte panel, first morning urine protein-to-creatinine ratio, serum albumin level, complement levels, and antinuclear antibodies (ANA). The child should be referred to a pediatric nephrologist for further evaluation and management. Renal biopsy is often necessary to establish a diagnosis and guide therapy.

In asymptomatic patients with low-grade proteinuria (urine protein-to-creatinine ratio between 0.2 and 1.0) in whom all other findings are normal, renal biopsy might not be indicated, because the underlying process may be transient or resolving or because specific pathologic

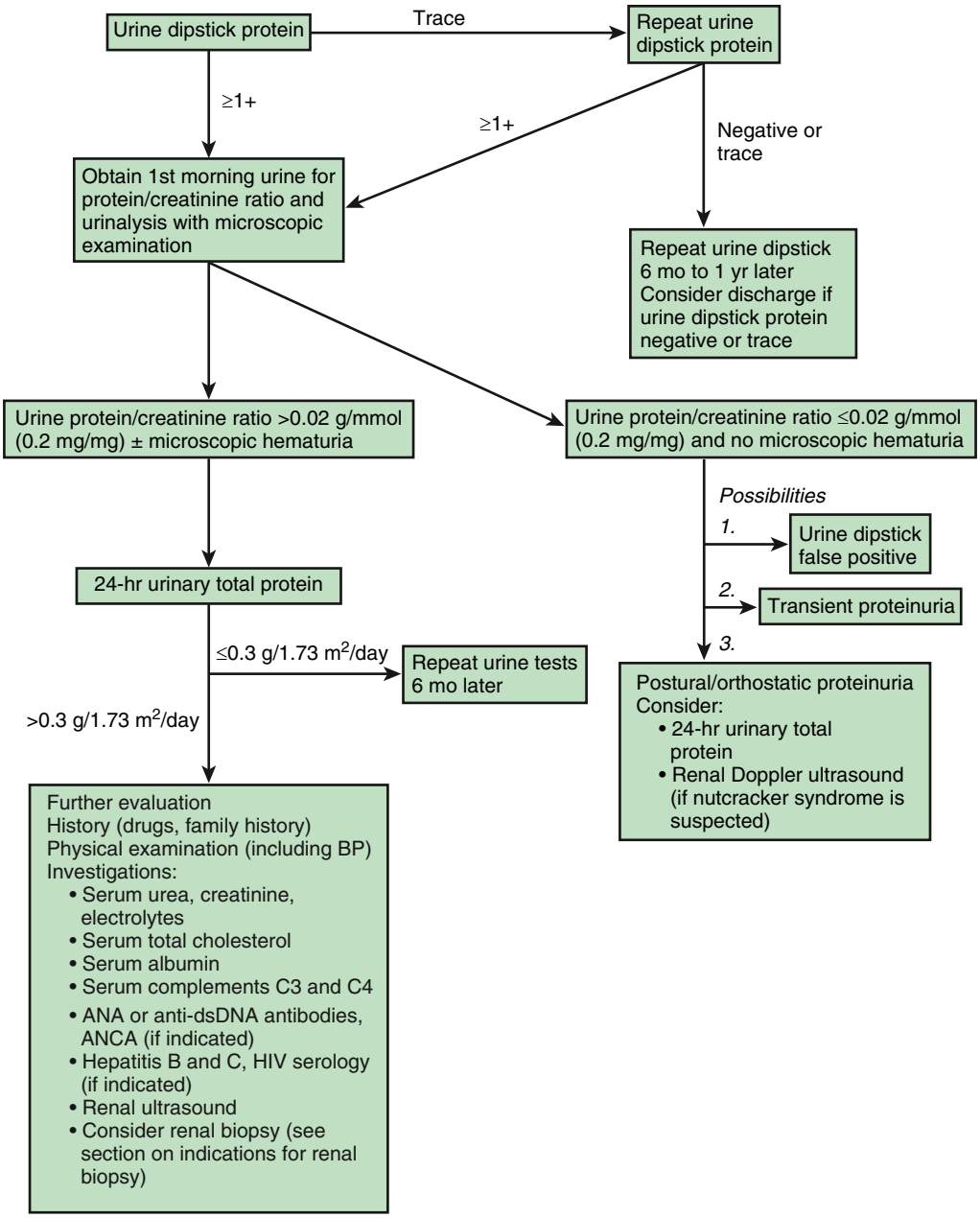

Fig 566.1 Algorithm for investigating proteinuria. ANA, Antinuclear antibody; ANCA, antinuclear cytoplasmic antibody; anti-dsDNA, anti–double-stranded DNA; BP, blood pressure. *(From Yap HK, Lau PYW. Hematuria and proteinuria. In: Geary DF, Scharfer F, eds. Comprehensive Pediatric Nephrology. Philadelphia: Elsevier; 2008: p. 190.)*

features of a chronic kidney disease might not yet be apparent. Such patients should have periodic reevaluation (ideally every 4-6 months unless the patient is or becomes symptomatic). The evaluation should consist of a physical examination with accurate blood pressure measurement, urinalysis, measurement of serum creatinine, and a repeat first morning urine protein-to-creatinine ratio. Indications for renal biopsy include increasing proteinuria (urine protein-to-creatinine ratio >1.0) or the development of hematuria with active urine sediment, hypertension, or reduced renal function.

TUBULAR PROTEINURIA

A variety of renal disorders that primarily involve the tubulointerstitial compartment of the kidney can cause low-grade fixed proteinuria (urine protein-to-creatinine ratio 0.2:1.0). In the healthy state, large amounts of proteins of lower molecular weight than albumin are filtered by the glomerulus and reabsorbed in the proximal tubule. Injury to the proximal tubules can result in diminished reabsorptive capacity and the loss of these low molecular weight proteins in the urine.

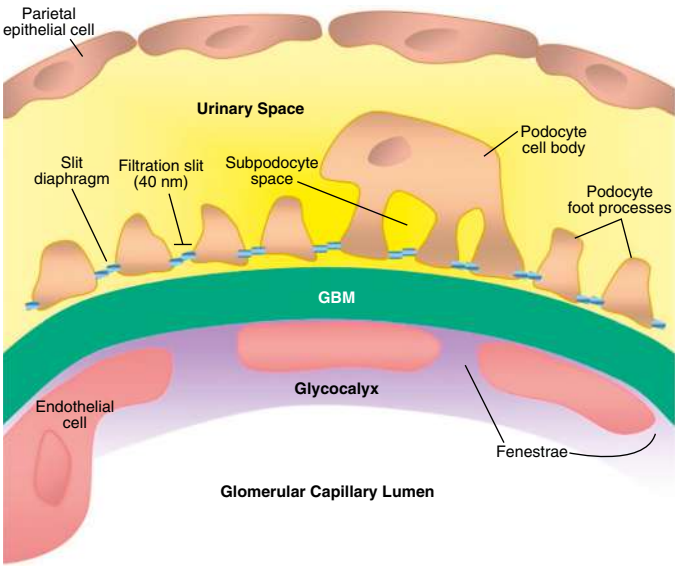

Fig. 566.2 Glomerular capillary wall. The three layers of the capillary wall (glomerular endothelial cell, glomerular basement membrane [GBM], and podocyte) act as the glomerular filtration barrier (GFB), preventing proteins and large molecules from passing from the capillary lumen into the urinary space. The podocyte cell body lies within the urinary space, and the cell is attached to the GBM through foot processes. Adjacent foot processes are separated by the filtration slit, bridged by the slit diaphragm. Disruption of the GFB leads the passage of protein across the capillary wall, leading to proteinuria. *(From Jefferson JA, Nelson PJ, Najafian B, et al. Podocyte disorders: core curriculum 2011. Am J Kidney Dis. 2011;58:666–677. Fig. 1.)*

Tubular proteinuria (see Table 566.1) may be seen in acquired and inherited disorders and may be associated with other defects of proximal tubular function, such as Fanconi syndrome (glycosuria, phosphaturia, bicarbonate wasting, and aminoaciduria). Tubular proteinuria is a consistent finding among patients with the X-linked tubular syndrome, Dent disease, caused by pathogenic variants of the renal chloride channel.

Asymptomatic patients having persistent proteinuria generally have glomerular rather than tubular proteinuria. In occult cases, glomerular and tubular proteinuria can be distinguished by protein electrophoresis of the urine. In tubular proteinuria, little or no albumin is detected, whereas in glomerular proteinuria, the major protein is albumin.

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Table 566.1 Causes of Proteinuria

TRANSIENT PROTEINURIA
Fever
Exercise
Dehydration
Cold exposure
Congestive heart failure
Seizure
Stress
Recent use of epinephrine
ORTHOSTATIC (POSTURAL) PROTEINURIA
GLOMERULAR DISEASES CHARACTERIZED BY ISOLATED PROTEINURIA
Idiopathic (minimal change) nephrotic syndrome
Focal segmental glomerulosclerosis
Secondary causes of nephrotic syndrome (see Chapter 567)
Mesangial proliferative glomerulonephritis
Membranous nephropathy
Membranoproliferative glomerulonephritis
Amyloidosis
Diabetic nephropathy
Sickle cell nephropathy
GLOMERULAR DISEASES WITH PROTEINURIA AS A PROMINENT FEATURE
Acute postinfectious glomerulonephritis (streptococcal, endocarditis, hepatitis B or C virus, HIV)
Immunoglobulin A nephropathy
IgA vasculitis nephritis
Lupus nephritis
Serum sickness
Alport syndrome
Vasculitic disorders
Reflux nephropathy
TUBULAR DISEASES
Cystinosis
Fanconi syndrome
Wilson disease
Lowe syndrome
Dent disease (X-linked recessive nephrolithiasis)
Galactosemia
Tubulointerstitial nephritis
Acute tubular necrosis
Renal dysplasia
Polycystic kidney disease
Reflux nephropathy
Renal transplant rejection
Drugs (aminoglycosides, cisplatin, penicillamine, lithium, nonsteroidal antiinflammatory drugs, cyclosporine)
Heavy metals (lead, gold, mercury)

Chapter 567

Nephrotic Syndrome

Elif Erkan

Nephrotic syndrome is the clinical manifestation of glomerular diseases associated with heavy (nephrotic range) proteinuria. Nephrotic-range proteinuria is defined as proteinuria >3.5 g/24 hr or a urine protein:creatinine ratio >2. The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of protein are hypoalbuminemia (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL).

Nephrotic syndrome affects 1-3 per 100,000 children <16 years of age. Without treatment, nephrotic syndrome in children is associated with a high risk of death, most commonly from infections. Fortunately, 80% of children with nephrotic syndrome respond to corticosteroid therapy. Although glucocorticoid therapy is standard therapy for nephrotic syndrome, neither the target cell nor the mechanism of action of steroids has been determined. Early referral to a pediatric nephrologist is recommended for initial management

of nephrotic syndrome. However, continued care of these children is always a collaborative effort between the nephrologist and the primary care physician.

ETIOLOGY

Most children with nephrotic syndrome have a form of **primary** or idiopathic nephrotic syndrome (Table 567.1). Glomerular lesions associated with idiopathic nephrotic syndrome include minimal change disease (most common), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis, C3 glomerulopathy, and membranous nephropathy (Table 567.2). These etiologies have different age distributions (Fig. 567.1). Nephrotic syndrome may also be **secondary** to systemic diseases such as systemic lupus erythematosus, IgA vasculitis (formerly Henoch-Schönlein purpura), malignancy (lymphoma and leukemia), and infections (hepatitis, HIV, and malaria) (see Table 567.1). A number of **hereditary** proteinuria syndromes are caused by pathogenic variants in genes that encode critical protein components of the glomerular filtration apparatus (Table 567.3).

PATHOGENESIS

Role of the Podocyte

The underlying abnormality in nephrotic syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The podocyte plays a crucial role in the development of proteinuria and the progression of glomerulosclerosis (Fig. 567.2). The podocyte is a highly differentiated epithelial cell located on the outside of the glomerular capillary loop. Foot processes are extensions of the podocyte that terminate on the glomerular basement membrane. The foot processes of a podocyte interdigitate with those from adjacent podocytes and are connected by a slit called the slit diaphragm. The podocyte functions as structural support of the capillary loop, is a major component of the glomerular filtration barrier to proteins, and is involved in synthesis and repair of the glomerular basement membrane. The slit diaphragm is one of the major impediments to protein permeability across the glomerular capillary wall. Slit diaphragms are not simple passive filters; they consist of numerous proteins that contribute to complex signaling pathways and play an important role in podocyte function. Important component proteins of the slit diaphragm include nephrin, podocin, CD2AP, and α-actinin 4. Podocyte injury or pathogenic variants of genes producing podocyte proteins may cause nephrotic-range proteinuria (see Table 567.3). Genetic screening of 1,655 patients with steroid-resistant nephrotic syndrome and congenital nephrotic syndrome in the European PodoNet Registry Cohort has shown that pathogenic variants in *NPHS1, WT1,* and *NPHS2* were the most common. The proportion of patients with pathogenic variants of podocyte genes decreased by age; it was 66% in patients with congenital nephrotic syndrome and 15–16% in school-age patients and adolescents.

In idiopathic, hereditary, and secondary forms of nephrotic syndrome, there are immune and nonimmune insults to the podocyte that lead to foot process effacement of the podocyte, a decrease in number of functional podocytes, and altered slit diaphragm integrity. The end result is increased protein leakiness across the glomerular capillary wall into the urinary space.

Role of the Immune System

Minimal change nephrotic syndrome (MCNS) may occur after viral infections and allergen challenges. MCNS has also been found to occur in children with Hodgkin lymphoma and T-cell lymphoma. That immunosuppression occurs with drugs such as corticosteroids and cyclosporine and provides indirect additional evidence that the immune system contributes to the overall pathogenesis of the nephrotic syndrome.

Considering the recurrence rate of 30% after kidney transplantation, a permeability factor was implicated in pathophysiology of FSGS. Rat glomeruli exposed to patient sera with FSGS has demonstrated increased permeability to albumin. A subset of adult and pediatric patients was found to have circulating nephrin autoantibodies, suggesting the role of circulating antibodies in the pathogenesis of MCNS.

CLINICAL CONSEQUENCES OF NEPHROTIC SYNDROME

Edema

Edema is the most common presenting symptom of children with nephrotic syndrome. Despite its almost universal presence, there is uncertainty as to the exact mechanism of edema formation. There are two opposing theories, the *underfill hypothesis* and the *overfill hypothesis,* that have been proposed as mechanisms causing nephrotic edema.

The *underfill hypothesis* is based on nephrotic-range proteinuria that leads to a fall in the plasma protein level with a corresponding decrease in intravascular oncotic pressure. This leads to leakage of plasma water into the interstitium, generating edema. As a result of reduced intravascular volume, there is increased secretion of vasopressin and atrial natriuretic factor, which, along with aldosterone, results in increased sodium and water retention by the tubules. Sodium and water retention therefore occur as a consequence of intravascular volume depletion.

This hypothesis does not fit the clinical picture of some patients with edema caused by nephrotic syndrome who have clinical signs of intravascular volume overload, not volume depletion. Treating these patients with albumin alone may not be sufficient to induce a diuresis without the concomitant use of diuretics. Also, reducing the renin-aldosterone axis with mineralocorticoid receptor antagonists does not result in a marked increase in sodium excretion. With the onset of remission of MCNS, many children will have increased urine output before their urinary protein excretion is measurably reduced.

The *overfill hypothesis* postulates that nephrotic syndrome is associated with primary sodium retention, with subsequent volume expansion and leakage of excess fluid into the interstitium. There is accumulating evidence that the epithelial sodium channel in the distal tubule may play a key role in sodium reabsorption in nephrotic syndrome. The clinical weaknesses of this hypothesis are evidenced by the numerous nephrotic patients who present with an obvious clinical picture of intravascular volume depletion: low blood pressure, tachycardia, and elevated hemoconcentration. Furthermore, amiloride, an epithelial sodium channel blocker, used alone is not sufficient to induce adequate diuresis.

The goal of therapy should be a gradual reduction of edema with judicious use of diuretics, sodium restriction, and cautious use of IV albumin infusions, if indicated.

Hyperlipidemia

There are several alterations in the lipid profile in children with nephrotic syndrome, including an increase in cholesterol, triglycerides, low-density lipoproteins, and very low-density lipoproteins. The high-density lipoprotein level remains unchanged or is low. In adults, this results in an increase in the adverse cardiovascular risk ratio, although the implications for children are not as serious, especially those with steroid-responsive nephrotic syndrome. Hyperlipidemia is thought to be the result of increased synthesis as well as decreased catabolism of lipids. Although commonplace in adults, the use of lipid-lowering agents in children is uncommon.

Increased Susceptibility to Infections

Children with nephrotic syndrome are especially susceptible to infections such as cellulitis, spontaneous bacterial peritonitis, and

Table 567.1 Causes of Childhood Nephrotic Syndrome

IDIOPATHIC NEPHROTIC SYNDROME
Minimal change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Glomerulonephritis associated with nephrotic syndrome–membranoproliferative glomerulonephritis, crescentic glomerulonephritis, immunoglobulin A nephropathy

GENETIC DISORDERS ASSOCIATED WITH PROTEINURIA OR NEPHROTIC SYNDROME (SEE ALSO TABLE 567.3)

Nephrotic Syndrome (Typical)
Finnish-type congenital nephrotic syndrome (absence of nephrin)
Focal segmental glomerulosclerosis (pathogenic variants in nephrin, podocin, *MYO1E*, α-actinin 4, TRPC6)
Diffuse mesangial sclerosis (pathogenic variants in laminin β_2 chain)
Denys-Drash syndrome (pathogenic variants in WT1 transcription factor)
Congenital nephrotic syndrome with lung and skin involvement (integrin α-3 pathogenic variant)
Mitochondrial disorders

Proteinuria With or Without Nephrotic Syndrome
Nail–patella syndrome (pathogenic variant in LMX1B transcription factor)
Alport syndrome (pathogenic variant in collagen biosynthesis genes)

Multisystem Syndromes With or Without Nephrotic Syndrome
Galloway-Mowat syndrome
Charcot-Marie-Tooth disease
Jeune syndrome
Cockayne syndrome
Laurence-Moon-Biedl-Bardet syndrome

Metabolic Disorders With or Without Nephrotic Syndrome
Alagille syndrome
α_1-Antitrypsin deficiency
Fabry disease
Glutaric acidemia
Glycogen storage disease
Hurler syndrome
Partial lipodystrophy
Mitochondrial cytopathies
Sickle cell disease

SECONDARY CAUSES OF NEPHROTIC SYNDROME

Infections
Endocarditis
Post-streptococcal
Hepatitides B, C
HIV-1
Infectious mononucleosis
Cytomegalovirus
Malaria
Syphilis (congenital and secondary)
Toxoplasmosis
Tuberculosis
Schistosomiasis
Filariasis

Drugs
Captopril
Penicillamine
Gold
Nonsteroidal antiinflammatory drugs
Pamidronate, other bisphosphonates
Interferon
Mercury
Heroin
Lithium
Rifampicin
Sulfasalazine

Immunologic or Allergic Disorders
Vasculitis syndromes
Castleman disease
Kimura disease
Bee sting
Snake venom
Food allergens
Serum sickness
Poison ivy, poison oak

ASSOCIATED WITH MALIGNANT DISEASE

Wilms Tumor
Lymphoma
Pheochromocytoma
Leukemia
Thymoma
Solid tumors

Glomerular Hyperfiltration
Oligomeganephronia
Morbid obesity
Adaptation to nephron reduction

Adapted from Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet*. 2003;362:629–638.

Table 567.2 Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome

FEATURES	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				TYPE I	TYPE II
DEMOGRAPHICS					
Age (years)	2-6, some adults	2-10, some adults	40-50	5-15	5-15
Sex (male:female)	2:1	1.3:1	2:1	1:1	1:1
CLINICAL MANIFESTATIONS					
Nephrotic syndrome	100%	90%	80%	60%*	60%*
Asymptomatic proteinuria	0	10%	20%	40%	40%
Hematuria (microscopic or gross)	10–20%	60–80%	60%	80%	80%
Hypertension	10%	20% early	Infrequent	35%	35%

Table 567.2 Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome—cont'd

FEATURES	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				TYPE I	TYPE II
Rate of progression to renal failure	Does not progress	10 years	50% in 10-20 years	10-20 years	5-15 years
Associated conditions	Usually none	HIV, heroin use, sickle cell disease, reflux nephropathy	Renal vein thrombosis; medications; SLE; hepatitides B, C; lymphoma; tumors	None	Partial lipodystrophy
GENETICS	None except in congenital nephrotic syndrome (see Table 567.3)	Podocin, α-actinin 4, TRPC6 channel, INF-2, MYH-9	None	None	None
LABORATORY FINDINGS	Manifestations of nephrotic syndrome ↑ BUN in 15–30% Normal complement levels	Manifestations of nephrotic syndrome ↑ BUN in 20–40% Normal complement levels	Manifestations of nephrotic syndrome Normal complement levels	Low complement levels: C1, C4, C3-C9	Normal complement levels: C1, C4, low C3-C9
RENAL PATHOLOGY					
Light microscopy	Normal	Focal sclerotic lesions	Thickened GBM, spikes	Thickened GBM, proliferation	Lobulation
Immunofluorescence	Negative	IgM, C3 in lesions	Fine granular IgG, C3	Granular IgG, C3	C3 only
Electron microscopy	Foot process fusion	Foot process fusion	Subepithelial deposits	Mesangial and subendothelial deposits	Dense deposits
REMISSION ACHIEVED AFTER 8 WK OF ORAL CORTICOSTEROID THERAPY	90%	15–20%	Resistant	Not established/ resistant	Not established/ resistant

*Approximate frequency as a cause of idiopathic nephrotic syndrome. Approximately 10% of cases of adult nephrotic syndrome are a result of various diseases that usually manifest as acute glomerulonephritis.
↑, Elevated; C, complement; GBM, glomerular basement membrane; Ig, immunoglobulin; SLE, systemic lupus erythematosus.
Modified from Couser WG. Glomerular disorders. In: Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil Textbook of Medicine,* 19th ed. Philadelphia: WB Saunders; 1992. p. 560.

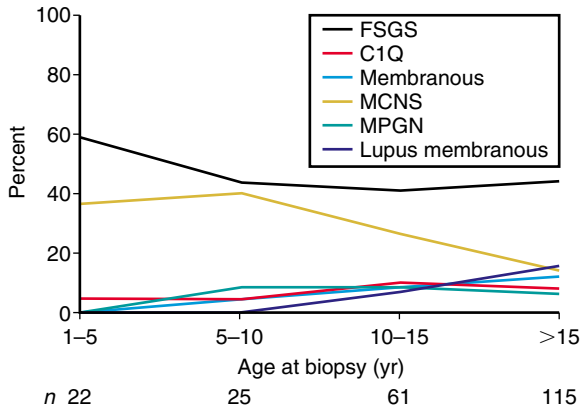

Fig. 567.1 Kidney biopsy results from 223 children with proteinuria referred for diagnostic kidney biopsy (Glomerular Disease Collaborative Network, J. Charles Jennette, MD, Hyunsook Chin, MS, and D.S. Gipson, 2007). C1Q, Nephropathy; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis; *n*, number of patients. *(From Gipson DS, Massengill SF, Yao L, et al. Management of childhood onset nephrotic syndrome. Pediatrics. 2009;124:747–757.)*

bacteremia. This occurs as a result of many factors, particularly hypoglobulinemia, as a result of the urinary losses of immunoglobulin (Ig) G. In addition, defects in the complement cascade from urinary loss of complement factors (predominantly C3 and C5), as well as alternative pathway factors B and D, lead to impaired opsonization of microorganisms. Children with nephrotic syndrome are at significantly increased risk for infection with encapsulated bacteria and, in particular, pneumococcal disease. **Spontaneous bacterial peritonitis** presents with fever, abdominal pain, and peritoneal signs. Although pneumococcus is the most frequent cause of peritonitis, gram-negative bacteria also are associated with a significant number of cases. Children with nephrotic syndrome and fever or other signs of infection must be evaluated aggressively, with appropriate cultures drawn, and should be treated promptly and empirically with antibiotics. Peritoneal leukocyte counts >250 cells/μL are highly suggestive of spontaneous bacterial peritonitis.

Hypercoagulability

Nephrotic syndrome is a hypercoagulable state resulting from multiple factors: vascular stasis from hemoconcentration and intravascular volume depletion, increased platelet number and aggregability, and changes in coagulation factor levels. There is an increase in hepatic production of fibrinogen along with urinary losses of antithrombotic factors such as antithrombin III and protein S. Deep venous thrombosis may occur in any venous bed, including the cerebral venous sinus, renal vein, and pulmonary veins. The clinical risk is low in children (2–5%) compared with adults but has the potential for serious consequences.

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Table 567.3 Causative Genes and Histologic Patterns of Nephrotic Syndrome by Time of Disease Onset

	CAUSE	INHERITANCE/ LOCUS	GENE/PROTEIN	HISTOLOGIC FEATURES
CONGENITAL ONSET (0-3 MO)				
Isolated	Congenital nephrotic syndrome of the Finnish type (CNF)	AR	*NPHS1*/nephrin	Radial dilation of proximal tubule
	Recessive SRNS, type 2	AR	*NPHS2*/podocin	FSGS/MGC
	Recessive SRNS, type 3	AR	*NPHS3*/PLCE1	DMS
	Isolated DMS	AR	WT1	DMS
	Recessive SRNS	AR	COQ2	FSGS, collapsing
	Recessive SRNS + deafness	AR	COQ6	FSGS
	Dominant SRNS + deafness	AD/11q24	Unknown	FSGS
	DMS + neurologic findings	AR	ARHGDIA/Rho GDP dissociation inhibitor (GDI) alpha	DMS
	NS + lung and skin disease	AR	*ITGA3*/integrin alpha 3	DMS
	Steroid-sensitive nephrotic syndrome	AR/2p12-13.2	Unknown	MGC/FSGS
Syndromic	Denys-Drash syndrome	AD	WT1	DMS
	Pierson syndrome	AR	*LAMB2*/laminin-β2	FSGS
	Nail–patella syndrome	AD	*LMX1B*/LIM homeobox transcription factor-1β	
	Frasier syndrome	AD	WT1	FSGS
	Schimke immunoosseous dysplasia	AR	SMARCAL1	FSGS
	Epidermolysis bullosa + FSGS	AR	*ITGB4*/integrin-β4	FSGS
	Galloway-Mowat syndrome	AR	Unknown	MGC to FSGS
INFANCY-CHILDHOOD ONSET				
Genetic	Recessive SSNS	AR	*EMP2*/epithelial membrane protein 2	
	Recessive SRNS	AR	*NPHS2*/podocin	FSGS/MGC
	Recessive SRNS	AR	*NPHS1*/nephrin	FSGS/MGC
	Recessive SRNS	AR	*NPHS3*/PLCE1	DMS
	Isolated DMS	AD	WT1	DMS
	Recessive SRNS + deafness or intellectual disability	AR	ARHGDIA	DMS
	SRNS	AR	*MYOE1*/nonmuscle class I myosin E	FSGS
	SRNS	AR	*PTPRO/GLEPP1* protein tyrosine phosphatase receptor type O/glomerular epithelial protein-1	FSGS
JUVENILE-ADULT ONSET				
Genetic	SRNS	AR or sporadic	*NPHS2* (p.R229Q)	FSGS
	Familial SRNS	AD	*INF2*/formin family of actin-regulating proteins	FSGS
	FSGS, type 1	AD/19q13	*ACTN4*/α-actinin-4	FSGS
	FSGS, type 2	AD/11q21-22	*TRPC6*/transient receptor potential cation channel, subfamily C, member 6	FSGS
	FSGS, type 3	AR-AD/6p12	*CD2AP*/CD2-associated protein	FSGS
	SRNS	AR	*PTPRO/GLEPP1* protein tyrosine phosphatase receptor type O/glomerular epithelial protein-1	FSGS
	SRNS	AR	*ADCK4*/aarF domain-containing kinase 4	FSGS
	SRNS (no extrarenal symptoms)	AD or sporadic	*LMX1B* encodes homeodomain-containing transcription factor	FSGS

AD, Autosomal dominant; AR, autosomal recessive; DMS, diffuse mesangial sclerosis; FSGS, focal segmental glomerulosclerosis; MGC, minimal glomerular changes; NS, nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome.
From Bakkaloglu SA, Schaefer F. Diseases of the kidney and urinary tract in children. In: Skorecki K, Chertow GM, Marsden PA, et al., eds. *Brenner & Rector's The Kidney*, 10th ed. Philadelphia: Elsevier; 2016: Table 74-2.

567.1 Idiopathic Nephrotic Syndrome

Elif Erkan

Approximately 90% of children with nephrotic syndrome have idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome is associated with primary glomerular disease without an identifiable causative disease or drug. Idiopathic nephrotic syndrome includes multiple histologic types: minimal change disease, mesangial proliferation, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis.

PATHOLOGY

In **minimal change nephrotic syndrome (MCNS)** (approximately 85% of total cases of nephrotic syndrome in children), the glomeruli appear normal or show a minimal increase in mesangial cells and matrix. Findings on immunofluorescence microscopy are typically negative, and electron microscopy simply reveals effacement of the

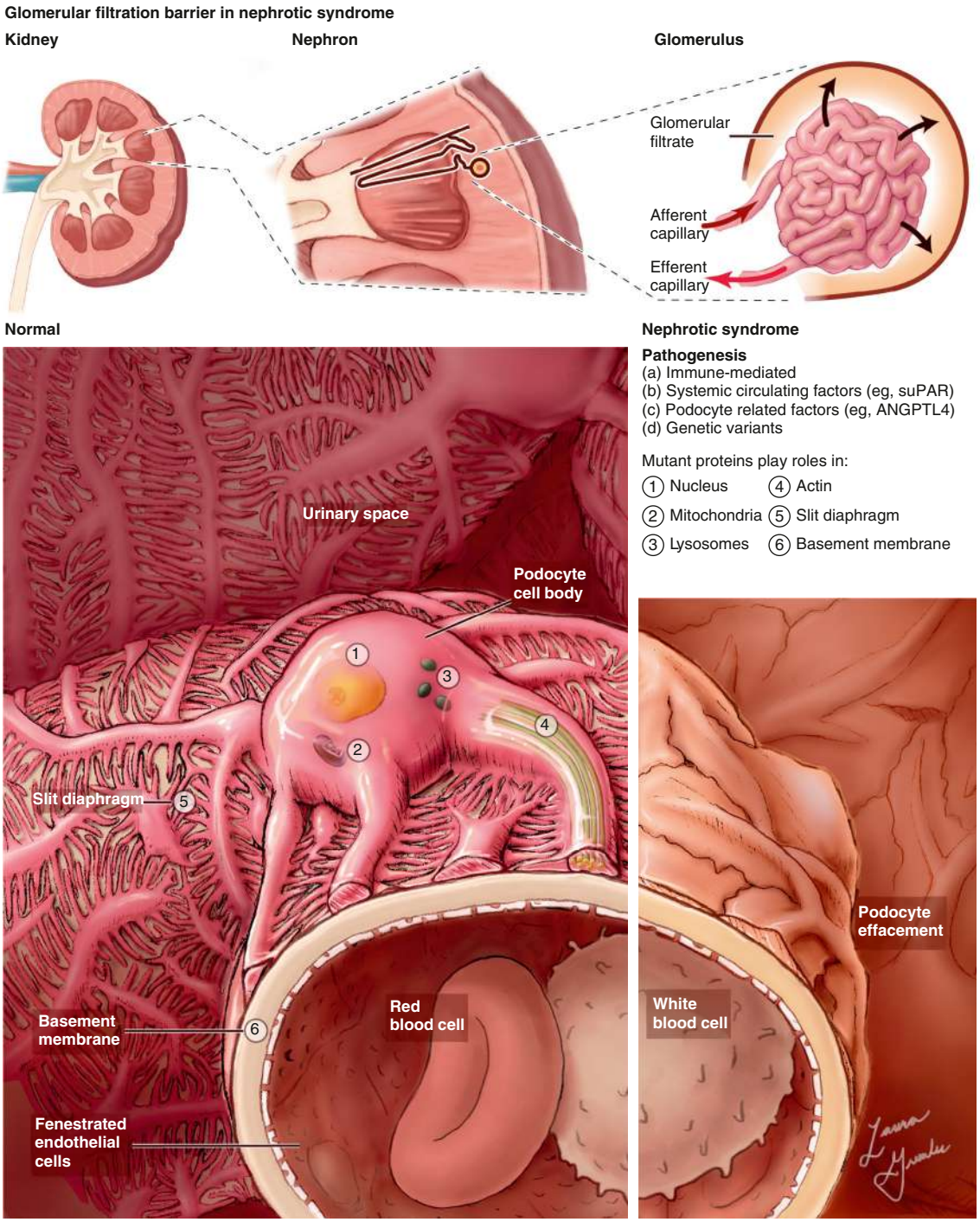

Fig. 567.2 The glomerular filtration barrier and pathogenesis of idiopathic nephrotic syndrome. Within the kidney is the glomerulus, a capillary tuft that filters the blood. The podocyte, glomerular basement membrane, and fenestrated glomerular endothelium form the glomerular filtration barrier, allowing the ultrafiltrate to enter the urinary space. The podocyte has extensive cellular extensions that interdigitate, and these foot processes are connected by the slit diaphragm. In nephrotic syndrome, there is extensive effacement of the podocytes and loss of this barrier to protein, allowing excessive serum albumin to leak into the urine. The pathogenesis of idiopathic nephrotic syndrome is hypothesized to be either immune mediated, due to a systemic podocyte-derived circulating factor, or, in rarer or familial forms, a genetic variant. Numerous pathogenic variants are associated with steroid-resistant nephrotic syndrome that affect various parts of the podocyte itself or the other constituents of the glomerular basement membrane. These include pathogenic variants affecting the podocyte nucleus, mitochondria or lysosomes, the slit diaphragm or actin cytoskeleton, and the glomerular basement membrane. Nephrin, podocin, and CD2AP, for example, are essential components of a zipper-like structure spanning the interdigitating foot processes of the podocyte and the slit diaphragm and link directly with the podocyte actin cytoskeleton. The actin cytoskeleton is further supported by microfilaments that maintain structural stability and facilitate the dynamic nature of the podocyte structure and function. The importance of these microfilaments is evident because pathogenic variants in both α-actinin 4 and INF2, which are involved in actin regulation and polymerization, lead to FSGS. *(From Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet. 2018;392:61–72. Fig. 2.)*

epithelial cell foot processes. More than 95% of children with minimal change disease respond to corticosteroid therapy.

Mesangial proliferation is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Immunofluorescence microscopy might reveal trace to 1+ mesangial IgM and/or IgA staining. Electron microscopy reveals increased numbers of mesangial cells and matrix as well as effacement of the epithelial cell foot processes. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy.

In **focal segmental glomerulosclerosis (FSGS),** glomeruli show lesions that are both focal (present only in a proportion of glomeruli) and segmental (localized to ≥1 intraglomerular tufts). The lesions consist of mesangial cell proliferation and segmental scarring on light microscopy (Fig. 567.3; see Table 567.2). Immunofluorescence microscopy is positive for IgM and C3 staining in the areas of segmental sclerosis. Electron microscopy demonstrates segmental scarring of the glomerular tuft with obliteration of the glomerular capillary lumen. The tip variant of FSGS is more common in Caucasians and is associated with better renal survival; by contrast, the collapsing variant of FSGS has a faster progression rate to end-stage kidney disease and is more common in Black patients.

Lesions consistent with FSGS may be seen secondary to HIV infection, vesicoureteral reflux, and IV use of heroin and other drugs of abuse. Only 20% of patients with FSGS respond to prednisone. The disease is often progressive, ultimately involving all glomeruli with end-stage kidney disease in most patients.

MINIMAL CHANGE NEPHROTIC SYNDROME

Clinical Manifestations

Idiopathic nephrotic syndrome is more common in males than in females (2:1) and most commonly appears between the ages of 2 and 6 years (see Fig. 567.1). However, it has been reported as early as 6 months of age and throughout adulthood. MCNS is present in 85–90% of patients <6 years of age. In contrast, only 20–30% of adolescents who present for the first time with nephrotic syndrome have MCNS. The more common cause of idiopathic nephrotic syndrome in this older age group is FSGS. The incidence of FSGS is increasing; it may be more common in Black, Hispanic, and Asian patients. FSGS is the most common cause of end-stage kidney disease in adolescents.

The initial episode of idiopathic nephrotic syndrome, as well as subsequent relapses, usually follows minor infections and, uncommonly, reactions to insect bites, bee stings, or poison ivy.

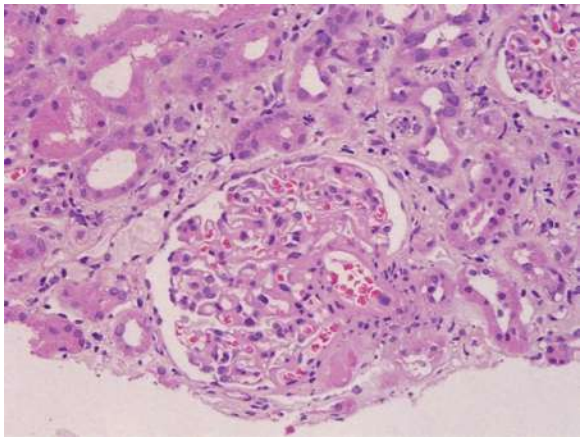

Fig. 567.3 Steroid-resistant nephrotic syndrome (SRNS). Kidney biopsy image of patient with SRNS shows focal segmental glomerulosclerosis. Segmental sclerosis is noted in a perihilar location with hyalinosis. Evidence of tubular atrophy and interstitial fibrosis is also present. H&E magnification 20×. *(From Tullus K, Webb H, Bagga A. Management of steroid-resistant nephrotic syndrome in children and adolescents. Lancet Child Adolesc Health. 2018;2:880–888. Fig. 1B, p. 881.)*

Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities. Nephrotic syndrome can initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema. Anorexia, irritability, abdominal pain, and diarrhea are common. Important features of MCNS are the absence of hypertension and gross hematuria (the so-called nephritic features).

The differential diagnosis of the child with marked edema includes protein-losing enteropathy, hepatic failure, heart failure, acute or chronic glomerulonephritis, and protein malnutrition. A diagnosis other than MCNS should be considered in children <1 year of age, with a positive family history of nephrotic syndrome, and/or the presence of extrarenal findings (e.g., arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency, and gross hematuria.

Diagnosis

Recommendations for the Initial Evaluation of Children with Nephrotic Syndrome

Confirming the Diagnosis of Nephrotic Syndrome. The initial workup for a child with nephrotic syndrome is shown in Table 567.4. Labs should be obtained including urinalysis with the first morning urine protein:creatinine ratio, CBC, serum electrolytes, BUN, creatinine, glomerular filtration rate, albumin, complement C3 and C4 levels, antinuclear and anti-streptococcal antibodies, and antineutrophil cytoplasmic antibodies.

The urinalysis reveals 3+ or 4+ proteinuria, and microscopic hematuria is present in 20% of children. A spot urine protein:creatinine ratio should be >2.0. The serum creatinine value is usually normal, but it may be abnormally elevated if there is diminished renal perfusion from contraction of the intravascular volume. The serum albumin level is <2.5 g/dL, and serum cholesterol and triglyceride levels are elevated. Serum complement levels are normal. Kidney ultrasound may be considered to exclude renal malformations and venous thrombosis but is not mandatory. A renal biopsy is not routinely performed if the patient fits the standard clinical picture of MCNS.

Treatment

Children with their first episode of nephrotic syndrome and mild to moderate edema may be managed as outpatients. Such outpatient management is not practiced in all major centers, because the time required for successful education of the family regarding all aspects of the condition can require a short period of hospitalization. The child's parents must be able to recognize the signs and symptoms of the complications of the disease and may be taught how to use a dipstick and interpret the results to monitor for the degree of proteinuria. Tuberculosis must be ruled out before starting immunosuppressive therapy with corticosteroids by placing a purified protein derivative skin test or obtaining an interferon-gamma release assay and confirming a negative result.

Children with onset of uncomplicated nephrotic syndrome between 1 and 12 years of age are likely to have steroid-responsive MCNS, and steroid therapy may be initiated without a diagnostic renal biopsy. Children with features that make MCNS less likely (gross hematuria, sustained hypertension, acute kidney injury, low C3 levels, arthritis and/or rash to suggest glomerulonephritis, or age <1 year or >12 years) should be considered for renal biopsy before treatment.

Use of Corticosteroids to Treat Minimal Change Nephrotic Syndrome

Corticosteroids are the mainstay of therapy for MCNS. The treatment guidelines for corticosteroid use presented in the following sections are adapted from and based on the 2021 Kidney Disease: Improving

Table 567.4 Investigations in a Child with Nephrotic Syndrome (NS)

BASELINE INVESTIGATIONS
1. Urinalysis and urine microscopy
2. Urine albumin or protein:creatinine ratio
3. 24-hr timed collection of urine for protein quantification
4. Serum electrolytes, albumin, total protein, renal function, and cholesterol
ADDITIONAL TESTING IF THERE IS A SUSPICION OF A GLOMERULONEPHRITIS
1. Serum complement C3 and C4 concentrations
2. Serum immunoglobulins
3. Antistreptolysin titers
4. Anti-DNase B antibodies
5. Antinuclear antigen antibodies
6. Anti–double-stranded DNA antibodies
7. Anti-neutrophil cytoplasmic antibodies
INFECTIOUS WORKUP DEPENDING ON CLINICAL CONTEXT
1. Hepatitis B and C, HIV, syphilis, or tuberculosis can also be considered depending on the clinical context
CONSIDERATION OF GENETIC TESTING
1. A positive family history of NS
2. Congenital NS
3. Failure to respond to steroid therapy
4. Persistent kidney dysfunction
5. Features suggestive of a known syndrome (appendix)
RENAL BIOPSY CONSIDERED IN THE FOLLOWING SITUATIONS
1. Age <1 or >12 years
2. Persistent or sustained elevation in creatinine
3. Significant hematuria or gross hematuria
4. Hypocomplementemia
5. Findings indicative of another autoimmune disease
6. Infection with hepatitis B or C, HIV, or tuberculosis
7. Hypertension
8. Glucocorticoid resistance

From Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *Lancet.* 2018;392:61–72. Panel 3.

Global Outcomes (KDIGO) clinical practice guidelines on glomerulonephritis (Fig. 567.4).

Treatment of the Initial Episode of Nephrotic Syndrome

In children with presumed MCNS, prednisone or prednisolone should be administered as a single daily dose of 60 mg/m^2/day or 2 mg/kg/day to a maximum of 60 mg daily for 4-6 weeks followed by alternate-day prednisone (starting at 40 mg/m^2 every other day or 1.5 mg/kg every other day) for a period ranging from 4-6 weeks. The issue of the duration of steroid treatment has been controversial, but current evidence suggests that prolonged (>12 weeks) glucocorticoid treatment increases the risk of adverse effects without further improving clinical outcomes. Approximately 80–90% of children respond to steroid therapy.

Response is defined as the attainment of remission within the initial 4 weeks of corticosteroid therapy. **Remission** consists of a urine protein:creatinine ratio of <0.2 or <1+ protein on urine dipstick testing for 3 consecutive days. Most children who respond to prednisone therapy do so within the first 5 weeks of treatment.

Managing the Clinical Sequelae of Nephrotic Syndrome

Edema. Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be hospitalized. In addition to sodium restriction (<1,500 mg daily), water/fluid restriction may be necessary if the child is hyponatremic. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity. Diuresis may be augmented by the administration of loop diuretics (furosemide), orally or intravenously, *although extreme caution should be exercised.* Aggressive diuresis can lead to intravascular volume depletion and an increased risk for acute renal failure and intravascular thrombosis.

When a patient has severe generalized edema with evidence of intravascular volume depletion (e.g., hemoconcentration, hypotension, tachycardia), IV administration of 25% albumin (0.5-1.0 g albumin/kg) as a slow infusion followed by furosemide (1-2 mg/kg/dose IV) is sometimes necessary. Such therapy should be used only in collaboration with a pediatric nephrologist and mandates close monitoring of volume status, blood pressure, serum electrolyte balance, and renal function. Symptomatic volume overload, with hypertension, heart failure, and pulmonary edema, is a potential complication of parenteral albumin therapy, particularly when it is administered as a rapid infusion.

Dyslipidemia. Dyslipidemia should be managed with a low-fat diet. Dietary fat intake should be limited to <30% of calories with a saturated fat intake of <10% calories. Dietary cholesterol intake should be <300 mg/day. There are insufficient data to recommend the use of 3-hydroxy-3-methylgluataryl coenzyme A (HMG-CoA) reductase inhibitors routinely in children with dyslipidemia.

Infections. Families of children with nephrotic syndrome should be counseled regarding the signs and symptoms of infections such as cellulitis, peritonitis, and bacteremia. If there is a suspicion of infection, a blood culture should be drawn before starting empiric antibiotic therapy. In the case of spontaneous bacterial peritonitis, peritoneal fluid should be collected if there is sufficient fluid to perform a paracentesis and sent for cell count, Gram stain, and culture. The antibiotic provided must be of broad enough coverage to include pneumococcus and gram-negative bacteria. A third-generation cephalosporin is a common choice of IV antibiotic.

Thromboembolism. Children who present with the clinical signs of thromboembolism should be evaluated with appropriate imaging studies to confirm the presence of a clot. Studies to delineate a specific underlying hypercoagulable state are recommended. In children with thrombotic events, anticoagulation therapy including heparin, low molecular weight heparin, and warfarin are therapeutic options that appear to be effective.

Obesity and Growth. Glucocorticoids may increase the body mass index in children who are overweight when steroid therapy is initiated, and these children are more likely to remain overweight. Anticipatory dietary counseling is recommended. Growth may be affected in children who require long-term corticosteroid therapy. Steroid-sparing strategies may improve linear growth in children who require prolonged courses of steroids.

Relapse of Nephrotic Syndrome. Relapse of nephrotic syndrome is defined as a urine protein:creatinine ratio of >2 or ≥3+ protein on urine dipstick testing for 3 consecutive days. Relapses are common, especially in younger children, and are often triggered by upper respiratory or gastrointestinal infections. Relapses are usually treated similar to the initial episode, except that daily prednisone courses are shortened. Daily high-dose prednisone is given until the child has achieved remission, and the regimen is then switched to alternate-day therapy. The duration of alternate-day therapy varies depending on the frequency of relapses of the individual child. Children are classified as infrequent relapsers or frequent relapsers, and as being steroid dependent, based on the number of relapses in a 12-month period or their inability to remain in remission following discontinuation of steroid therapy.

Steroid Resistance. Steroid resistance is defined as the failure to achieve remission after 4 weeks of corticosteroid therapy. Children with steroid-resistant nephrotic syndrome require further evaluation, including a diagnostic kidney biopsy and genetic testing. Steroid-resistant nephrotic syndrome is usually caused by FSGS (80%), MCNS, or membranoproliferative glomerulonephritis.

Implications of Steroid-Resistant Nephrotic Syndrome. Steroid-resistant nephrotic syndrome, and specifically FSGS, is associated with a 50% risk for end-stage kidney disease within 5 years of diagnosis if patients do not achieve a partial or complete remission. Persistent nephrotic syndrome is associated with a poor

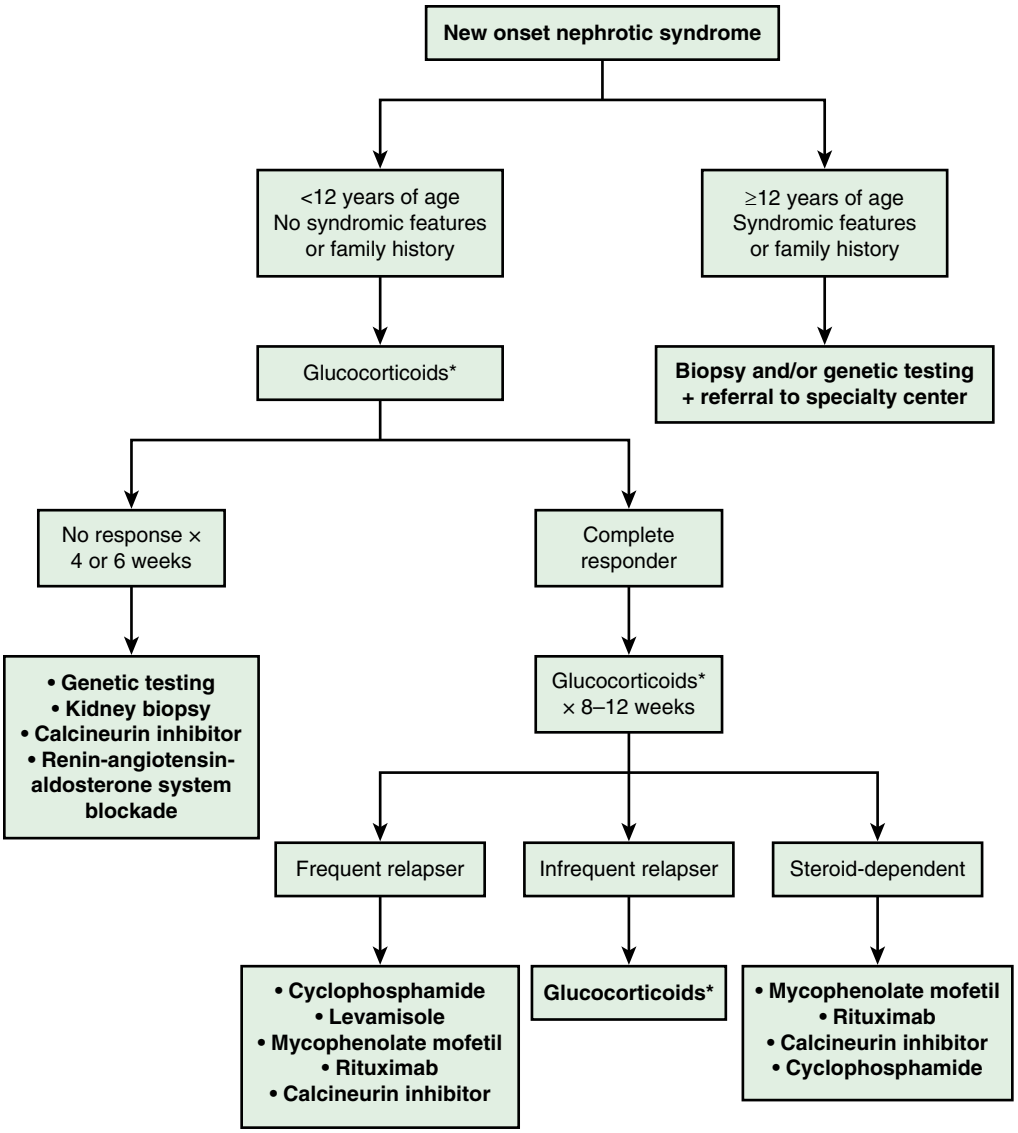

Fig. 567.4 Treatment algorithm for new-onset nephrotic syndrome (NS). Therapeutic approach to NS in children from onset. *Glucocorticoids include PO prednisone or prednisolone. NS, Nephrotic syndrome. *(From Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100[4S]:S1–S276. Fig. 40.)*

patient-reported quality of life, hypertension, serious infections, and thromboembolic events. Children reaching end-stage kidney disease have a greatly reduced life expectancy compared with their peers.

Alternative Therapies to Corticosteroids in the Treatment of Nephrotic Syndrome. Steroid-dependent patients, frequent relapsers, and steroid-resistant patients are candidates for alternative therapies, particularly if they have severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/or growth failure). **Cyclophosphamide** prolongs the duration of remission and reduces the number of relapses in children with **frequently relapsing** and **steroid-dependent** nephrotic syndrome. The potential side effects of the drug (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy) should be carefully reviewed with the family before initiating treatment. Cyclophosphamide (2 mg/kg) is given as a single oral dose for a total duration of 8-12 weeks. Alternate-day prednisone therapy is often continued during cyclophosphamide administration. During cyclophosphamide therapy, the white blood cell count must be monitored weekly, and the drug should be withheld if the count falls below 5,000/mm^3. The cumulative threshold dose above which oligospermia or azoospermia occurs in males is >250 mg/kg.

Calcineurin inhibitors (cyclosporine or tacrolimus) are recommended as initial therapy for children with **steroid-resistant** nephrotic syndrome. Children must be monitored for side effects, including hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia. **Mycophenolate** can maintain remission in children with steroid-dependent or frequently relapsing nephrotic syndrome. **Levamisole**, an anthelmintic agent with immunomodulating effects that has been shown to reduce the risk of relapse when compared with prednisone, is not available in the United States.

Rituximab, the chimeric monoclonal antibody against CD20-targeting B cells, was found to be effective in children by maintaining remission and decreasing the number of relapses in steroid-dependent and/or steroid-resistant nephrotic syndrome. Randomized trials with rituximab have shown promising results of an up to 80% drug-free remission rate at 1 year in patients with steroid-dependent nephrotic syndrome. However, rituximab is less effective in patients treated with calcineurin inhibitors and steroids and with multidrug-resistant nephrotic syndrome.

Most children who respond to cyclosporine, tacrolimus, or mycophenolate therapy tend to relapse when the medication is discontinued. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may be helpful as adjunct therapy to reduce proteinuria in steroid-resistant patients.

Immunizations in Children with Nephrotic Syndrome. To reduce the risk of serious infections in children with nephrotic syndrome, give the full pneumococcal vaccination (with the 13-valent conjugant vaccine and 23-valent polysaccharide vaccine) and influenza vaccination annually to the child and their household contacts; defer vaccination with live vaccines until the prednisone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days. Live virus vaccines are contraindicated in children receiving corticosteroid-sparing agents such as cyclophosphamide or cyclosporine. Following close contact with varicella infection, give immunocompromised children taking immunosuppressive agents varicella-zoster immune globulin if available; immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child, but avoid direct exposure of the child to gastrointestinal or respiratory secretions of vaccinated contacts for 3-6 weeks after vaccination.

Table 567.5 provides monitoring recommendations for children with nephrotic syndrome.

Prognosis

Most children with steroid-responsive nephrotic syndrome have repeated relapses, which generally decrease in frequency as the child grows older. Although there is no proven way to predict an individual child's course, children who respond rapidly to steroids and those who have no relapses during the first 6 months after diagnosis are likely to follow an infrequently relapsing course. It is important to indicate to the family that the child with steroid-responsive nephrotic syndrome is unlikely to develop chronic kidney disease, that the disease is rarely hereditary, and that the child (in the absence of prolonged cyclophosphamide therapy) will remain fertile. To minimize the psychologic effects of the condition and its therapy, children with idiopathic nephrotic syndrome should not be considered chronically ill and should participate in all age-appropriate childhood activities and maintain an unrestricted diet when in remission.

Children with steroid-resistant nephrotic syndrome, most often caused by FSGS, generally have a much poorer prognosis. These children develop progressive renal insufficiency, ultimately leading to end-stage kidney disease requiring dialysis or kidney transplantation. Recurrent nephrotic syndrome develops in 30–50% of transplant recipients with FSGS.

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567.2 Secondary Nephrotic Syndrome

Elif Erkan

Nephrotic syndrome can occur as a secondary feature of many forms of glomerular disease. Membranous nephropathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, lupus nephritis, and IgA vasculitis nephritis (formerly Henoch-Schönlein purpura nephritis) can all have a nephrotic component (see Tables 567.1 and 567.3). Secondary nephrotic syndrome should be suspected in patients >12 years and those with sustained hypertension, hematuria, renal dysfunction, extrarenal symptoms (e.g., rash, arthralgias, fever), or depressed serum complement levels. In certain areas of the world, malaria and schistosomiasis are the leading causes of nephrotic syndrome. Other infectious agents associated with nephrotic syndrome include hepatitis B virus, hepatitis C virus, filaria, leprosy, and HIV.

Nephrotic syndrome has been associated with malignancy, particularly in the adult population. In patients with solid tumors, such as carcinomas of the lung and gastrointestinal tract, the renal pathology often resembles membranous glomerulopathy. Immune complexes composed of tumor antigens and tumor-specific antibodies presumably mediate the renal involvement. In patients with lymphomas, particularly Hodgkin lymphoma, the renal pathology most often resembles MCNS. The proposed mechanism of

Table 567.5 Monitoring Recommendations for Children with Nephrotic Syndrome

DISEASE AND TREATMENT	HOME URINE PROTEIN	WEIGHT, GROWTH, BMI	BP	CR	ELECTROLYTES	SERUM GLUCOSE	CBC	LIPID PROFILE	DRUG LEVELS	LFTS	UA	CPK
DISEASE TYPE												
Mild (steroid responsive)	•	•	•								•	
Moderate (frequent relapsing, steroid dependent)	•	•	•	•				•			•	
Severe (steroid resistant)	•	•	•	•				•			•	
THERAPY												
Corticosteroids		•	•			•		•				
Cyclophosphamide				•			•				•	
Mycophenolate mofetil							•			•		
Calcineurin inhibitors			•	•	•	•		•	•			
ACEIs/ARBs			•	•	•		•					
HMG-CoA reductase inhibitors								•		•		•

ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CPK, creatine phosphokinase; Cr, creatinine; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LFTs, liver function tests; UA, urinalysis.

From Gipson DS, Massengill SF, Yao L, et al. Management of childhood onset nephrotic syndrome. *Pediatrics*. 2009;124:747–757.

the nephrotic syndrome is that the lymphoma produces a lymphokine that increases permeability of the glomerular capillary wall. Nephrotic syndrome can develop before or after the malignancy is detected, resolve as the tumor regresses, and return if the tumor recurs.

Nephrotic syndrome has also developed during therapy with numerous drugs and chemicals. The histologic picture can resemble membranous glomerulopathy (penicillamine, captopril, gold, nonsteroidal antiinflammatory drugs, mercury compounds), MCNS (probenecid, ethosuximide, methimazole, lithium), or proliferative glomerulonephritis (procainamide, chlorpropamide, phenytoin, trimethadione, paramethadione).

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567.3 Congenital Nephrotic Syndrome

Elif Erkan

Nephrotic syndrome (massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia) has a poorer prognosis when it occurs in the first year of life, when compared with nephrotic syndrome manifesting in childhood. **Congenital nephrotic syndrome** is defined as nephrotic syndrome manifesting at birth or within the *first 3 months of life.* Congenital nephrotic syndrome may be classified as primary or as secondary to a number of etiologies such as in utero infections (cytomegalovirus, toxoplasmosis, syphilis, hepatitides B and C, HIV), infantile systemic lupus erythematosus, or mercury exposure.

Primary congenital nephrotic syndrome is due to a variety of syndromes inherited as autosomal recessive disorders (see Table 567.3). A number of structural and functional abnormalities of the glomerular filtration barrier causing congenital nephrotic syndrome have been elucidated. In a large European cohort of children with congenital nephrotic syndrome, 85% carried pathogenic variants in four genes *(NPHS1, NPHS2, WT1,* and *LAMB2),* the first three of which encode components of the glomerular filtration barrier. The Finnish type of congenital nephrotic syndrome is caused by pathogenic variants in the *NPHS1* or *NPHS2* gene, which encodes nephrin and podocin, critical components of the slit diaphragm. Affected infants most commonly present at birth with edema caused by massive proteinuria, and they are typically delivered with an enlarged placenta (>25% of the infant's weight). Severe hypoalbuminemia, hyperlipidemia, and hypogammaglobulinemia result from loss of filtering selectivity at the glomerular filtration barrier. Prenatal diagnosis can be made by the presence of elevated maternal and amniotic α-fetoprotein levels.

Denys-Drash syndrome is caused by pathogenic variants in the *WT1* gene, which results in abnormal podocyte function. Patients present with early-onset nephrotic syndrome, progressive renal insufficiency, ambiguous genitalia, and Wilms tumor.

Pathogenic variants in the *LAMB2* gene, seen in **Pierson syndrome,** lead to abnormalities of β_2-laminin, a critical component of the glomerular and ocular basement membranes. In addition to congenital nephrotic syndrome, affected infants display bilateral microcoria (fixed narrowing of the pupil).

Galloway-Mowat syndrome is characterized by microcephaly with hiatal hernia and congenital nephrotic syndrome. Patients have distinctive kidney biopsy findings with loss of or poor basement membrane formation or permeation of their basement membranes with fibrils.

Regardless of the etiology of congenital nephrotic syndrome, the diagnosis is made clinically in newborns or infants who demonstrate severe generalized edema, poor growth and nutrition with hypoalbuminemia, increased susceptibility to infections, hypothyroidism (from urinary loss of thyroxin-binding globulin), and an increased risk of thrombotic events (urinary loss of antithrombin). Most infants have progressive renal insufficiency.

Table 567.6 Causes of Nephrotic Syndrome in Infants Younger Than 1 Year of Age

SECONDARY CAUSES
Infections
Syphilis
Cytomegalovirus
Toxoplasmosis
Rubella
Hepatitis B or C
HIV
Malaria
Drug Reactions
Toxins
Mercury
Syndromes with Associated Renal Disease
Nail–patella syndrome
Lowe syndrome
Nephropathy associated with congenital brain malformation
Denys-Drash syndrome: Wilms tumor
Hemolytic uremic syndrome
Systemic lupus erythematosus
PRIMARY CAUSES (SEE TABLE 567.3)
Congenital nephrotic syndrome
Diffuse mesangial sclerosis
Minimal change disease
Focal segmental sclerosis
Membranous nephropathy

From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004: p. 418.

Albumin and diuretic infusions, providing high amounts of protein (3-4 g/kg), lipids, and a high caloric intake to maintain nutrition, along with vitamin and thyroid hormone replacement, have been the mainstream therapy for congenital nephrotic syndrome. Treatment of the congenital syndrome also consists of unilateral nephrectomy and use of angiotensin-converting enzyme inhibitors and/or indomethacin to decrease the proteinuria and glomerular filtration rate. Some centers prefer more aggressive therapy, including bilateral nephrectomy at 1-2 years of age, weight >7 kg, and initiation of peritoneal dialysis with subsequent kidney transplantation.

Secondary congenital nephrotic syndrome can resolve with treatment of the underlying cause, such as syphilis (Table 567.6). The management of primary congenital nephrotic syndrome includes intensive supportive care with IV albumin and diuretics, regular administration of IV γ-globulin, and aggressive nutritional support (often parenteral), while attempting to pharmacologically decrease urinary protein loss with angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, and prostaglandin synthesis inhibitors, or even unilateral nephrectomy. If conservative management fails and patients suffer from persistent anasarca or repeated severe infections, bilateral nephrectomies are performed, and chronic dialysis is initiated. Renal transplantation is the definitive treatment of congenital nephrotic syndrome, though recurrence of the nephrotic syndrome has been reported to occur after transplantation.

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Section 4

Tubular Disorders

Chapter 568

Tubular Function

Eliza Blanchette and Bradley P. Dixon

Water and electrolytes are freely filtered at the level of the glomerulus. Thus the electrolyte content of ultrafiltrate at the beginning of the proximal tubule is similar to that of plasma. Carefully regulated processes of tubular reabsorption and/or tubular secretion determine the final water content and electrolyte composition of urine. Bulk movement of solute tends to occur in the proximal portions of the nephron, and fine adjustments tend to occur distally (see Chapter 73).

SODIUM

Sodium is essential in maintaining extracellular fluid balance and, thus, volume status. The kidney is capable of effecting large changes in sodium excretion in a variety of normal and pathologic states.

There are four main sites of sodium transport. Approximately 60% of sodium is absorbed in the proximal tubule by coupled transport with glucose, amino acids, and phosphate; 25% in the ascending loop of Henle (mediated by NKCC2, the loop diuretic-sensitive sodium-potassium-2 chloride transporter); and 15% in the distal tubule (mediated by NCCT, the thiazide-sensitive sodium chloride co-transporter) and collecting tubule (mediated by ENaC, the epithelial sodium channel).

The urinary excretion of sodium normally approximates the sodium intake of 2-6 mEq/kg/24 hr for a child consuming a typical American diet, minus 1-2 mEq/kg/24 hr required for normal metabolic processes. However, in states of volume depletion (dehydration, blood loss) or decreased effective circulating blood volume (septic shock, hypoalbuminemic states, heart failure), there may be a dramatic decrease in urinary sodium excretion to as low as 1 mEq/L. Changes in systemic volume status are detected by (1) baroreceptors in the atria, afferent arteriole, and carotid sinus and (2) by the macula densa, which detects changes in chloride delivery.

The major hormonal mechanisms mediating sodium balance include the renin-angiotensin-aldosterone axis, atrial natriuretic factor, and norepinephrine. Angiotensin II and aldosterone increase sodium reabsorption in the proximal tubule and distal tubule, respectively. Norepinephrine, released in response to volume depletion, does not directly act on tubular transport mechanisms but affects sodium balance by decreasing renal blood flow, thus decreasing the filtered load of sodium as well as stimulating renin release. With more severe volume depletion, antidiuretic hormone is also released (see Chapter 570). Sodium excretion is promoted by atrial natriuretic factor and suppression of renin.

POTASSIUM

Extracellular potassium homeostasis is regulated because small changes in plasma potassium concentrations have dramatic effects on cardiac, neural, and neuromuscular function (see Chapter 73.4). Essentially, all filtered potassium is fully reabsorbed in the proximal tubule and ascending loop of Henle. Therefore urinary excretion of potassium is completely dependent on tubular secretion by potassium channels (renal outer medullary potassium [ROMK] and big potassium [BK] channels) present in the principal cells of the collecting tubule. Factors that promote potassium secretion include aldosterone, increased sodium delivery to the distal nephron, and increased urine flow rate.

CALCIUM

A significant portion of filtered calcium (70%) is reabsorbed in the proximal tubule. Additional calcium is reabsorbed in the ascending loop of Henle (20%) and the distal tubule and collecting duct (5–10%). Calcium is reabsorbed by passive movement between cells (paracellular absorption) in a process driven by sodium chloride reabsorption and potassium recycling into the lumen. In addition, calcium uptake is actively regulated by calcium receptors, specific transporters, and calcium channels. Factors that promote calcium reabsorption include parathyroid hormone (released in response to hypocalcemia), calcitonin, vitamin D, thiazide diuretics, and volume depletion (see Chapter 610). Factors that promote calcium excretion include volume expansion, increased sodium intake, and diuretics such as mannitol and furosemide.

PHOSPHATE

The majority of filtered phosphate is reabsorbed in the proximal tubule by active transport coupled with sodium through the NaPi2a, NaPi2c, and PiT-2 channels. Reabsorption is increased by dietary phosphorus restriction, volume contraction, and growth hormone. Fibroblast growth factor 23 (FGF-23), parathyroid hormone, and volume expansion increase phosphate excretion.

MAGNESIUM

Approximately 25% of filtered magnesium is reabsorbed in the proximal tubule. Modulation of renal magnesium excretion occurs primarily in the ascending loop of Henle, with some contribution of the distal convoluted tubule. Magnesium is transported by the paracellular route similar to calcium, as well as through the transcellular route. Although specific magnesium transporters for transcellular absorption have been identified such as TRPM6, the precise mechanisms by which they are regulated remain unclear.

ACIDIFICATION AND CONCENTRATING MECHANISMS

Acidification and concentration are addressed in the sections on renal tubular acidosis and nephrogenic diabetes insipidus, respectively (see Chapters 569 and 570).

DEVELOPMENTAL CONSIDERATIONS

The tubular transport capabilities of neonates (especially premature infants) and young infants are less than those of adults. Although nephrogenesis (the formation of new glomerular/tubular units) is complete by about 36 weeks of gestation, significant tubular maturation occurs during infancy. Renal tubular immaturity, a reduced glomerular filtration rate, a decreased concentrating gradient, and a diminished responsiveness to antidiuretic hormone are characteristic of young infants. These factors can contribute to impaired regulation of water, solute, and electrolyte and acid-base homeostasis, particularly during times of acute illness.

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Chapter 569

Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

Renal tubular acidosis (RTA) is a disease state characterized by a non–anion gap (hyperchloremic) metabolic acidosis in the setting of a normal or near-normal glomerular filtration rate. There are four main types of RTA: proximal (type II), classic distal (type I), hyperkalemic (type IV), and a combined proximal and distal (type III). Proximal RTA (pRTA) results from impaired bicarbonate reabsorption and distal RTA (dRTA) from failure to secrete acid. These defects may be inherited and persistent from birth or acquired, as is seen more commonly in clinical practice.

NORMAL URINARY ACIDIFICATION

Kidneys contribute to the acid-base balance by reabsorption of filtered bicarbonate (HCO_3^-) and excretion of hydrogen ion (H^+) produced every day. Hydrogen ion secretion from tubule cells into the lumen is key in the reabsorption of HCO_3^- and the formation of titratable acid (H^+ bound to buffers such as HPO_4^{2-}) and ammonium ions (NH_4^+). Because loss of filtered HCO_3^- is equivalent to the addition of H^+ to the body, all filtered bicarbonate should be absorbed before dietary H^+ can be excreted. Approximately 90% of filtered bicarbonate is absorbed in the proximal tubule and the remaining 10% in the distal segments, mostly the thick ascending limb and outer medullary collecting tubule (Fig. 569.1). In the proximal tubule and thick ascending limb of the loop of Henle, H^+ from water is secreted by the Na^+-H^+ exchanger on the luminal membrane. H^+ combines with filtered bicarbonate, resulting in the formation of H_2CO_3, which decomposes into water and CO_2 in the presence of carbonic anhydrase IV. CO_2 diffuses freely back into the cell, combines with OH^- (from H_2O) to form HCO_3^- in the presence of carbonic anhydrase II, and returns to the systemic circulation via a Na^+-HCO_3^- co-transporter situated at the basolateral membrane of the cell. In the collecting tubule, H^+ is secreted into the lumen by H^+ATPase (adenosine triphosphatase), and HCO_3^- is returned to the systemic circulation by the HCO_3^--Cl^- exchanger located on the basolateral membrane. The H^+ secreted proximally and distally in excess of the filtered HCO_3^- is excreted in the urine either as titratable acid ($H_2PO_4^-$) or as NH_4^+.

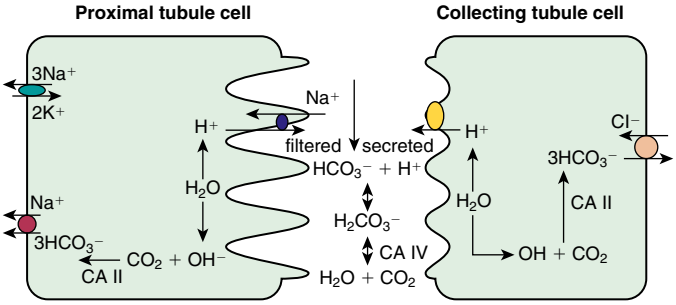

Fig. 569.1 Major cellular luminal events in acid-base regulation in the proximal and collecting tubule cells. In the proximal tubule, H^+, split from H_2O, is secreted into the lumen via the Na^+/H^+ exchanger, and HCO_3^-, formed by a combination of OH^- (split from H_2O) with CO_2 in the presence of carbonic anhydrase (CA) II, is returned to the systemic circulation by an Na^+-$3HCO_3^-$ co-transporter. Similarly, in the collecting tubule, H^+ is secreted into the lumen by an active H^+-ATPase (adenosine triphosphatase), and HCO_3^- is returned to the systemic circulation via an HCO_3^--Cl^- exchanger. H^+ secreted into the lumen combines with filtered HCO_3^- to form carbonic acid (H_2CO_3) and then CO_2 and H_2O in the presence of CA IV, which can be passively reabsorbed. *(Modified from Rose BD, Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed. New York: McGraw-Hill; 2001.)*

569.1 Proximal (Type II) Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

pRTA can be inherited and persistent from birth or occur as a transient phenomenon during infancy. Although rare, it may be primary and isolated. Typically, however, pRTA occurs as a component of global proximal tubular dysfunction or **Fanconi syndrome,** which is characterized by low molecular weight proteinuria, glycosuria, phosphaturia, aminoaciduria, and pRTA. Table 569.1 outlines the causes of pRTA and Fanconi syndrome. Many of these causes are inherited disorders. In addition to **cystinosis** and **Lowe syndrome,** autosomal recessive and dominant pRTA are addressed further in this section. Other inherited forms of Fanconi syndrome include galactosemia (see Chapter 107.2), hereditary fructose intolerance (see Chapter 107.3), tyrosinemia (see Chapter 105.2), and Wilson disease (see Chapter 405.2). Dent disease, or X-linked nephrolithiasis, is discussed in Chapter 571.3. In children, an important form of secondary Fanconi syndrome is exposure to medications such as the chemotherapy agents ifosfamide and cisplatin.

AUTOSOMAL RECESSIVE DISEASE

Isolated autosomal recessive pRTA is caused by pathogenic variants in *SLC4A4* encoding the sodium bicarbonate co-transporter NBC1. It manifests with ocular abnormalities (band keratopathy, cataracts, and glaucoma, often leading to blindness), short stature, enamel defects of the teeth, intellectual impairment, and occasionally basal ganglia calcification along with pRTA. An autosomal dominant pattern of inheritance has also been identified but is rare; these patients present with hyperchloremic metabolic acidosis, a normal ability to acidify urine, normal renal function, and growth retardation.

CLINICAL MANIFESTATIONS OF PROXIMAL RTA AND FANCONI SYNDROME

Patients with isolated, sporadic, or inherited pRTA present with growth failure in the first year of life. Additional symptoms can include polyuria, dehydration (from sodium loss), anorexia, vomiting, constipation, and hypotonia. Patients with primary Fanconi syndrome have additional symptoms, secondary to phosphate wasting, such as rickets. Those with systemic diseases present with additional signs and symptoms specific to their underlying disease. Urinalysis in patients with isolated pRTA is generally unremarkable. The urine pH is acidic (<5.5) because distal acidification mechanisms are intact in these patients. Urinary studies in patients with Fanconi syndrome demonstrate varying degrees of phosphaturia, aminoaciduria, glycosuria, uricosuria, and elevated urinary sodium or potassium. Depending on the nature of the underlying disorder, laboratory evidence of chronic kidney disease (CKD), including elevated serum creatinine, may be present.

Cystinosis

Cystinosis is an autosomal recessive, systemic lysosomal storage disease caused by a defect in the transport of cystine out of lysosomes resulting in the accumulation of cystine crystals in most of the major organs of the body, notably the kidney, liver, eye, and brain. It occurs at an incidence of 1:100,000 to 1:200,000. At least three clinical patterns have been described. The most severe form of the disease, infantile or nephropathic cystinosis, presents in the first or second

Table 569.1 Disorders with Dysfunction of Renal Acidification—Defective HCO_3^- Reclamation: Proximal Renal Tubular Acidosis

ISOLATED PURE BICARBONATE WASTING (UNASSOCIATED WITH FANCONI SYNDROME)
Primary
Autosomal recessive with ocular abnormalities (pathogenic variant of *SLC4A4*/NBC1)
Autosomal dominant with short stature (pathogenic variant of *SLC9A3*/ NHE3)
Carbonic anhydrase deficiency, inhibition, or alteration
Drugs
Acetazolamide
Topiramate
Sulfanilamide
Mafenide acetate
Carbonic anhydrase II deficiency with osteopetrosis (mixed proximal and distal RTA type III)
GENERALIZED (ASSOCIATED WITH FANCONI SYNDROME)
Primary (Without Associated Systemic Disease)
Genetic
Sporadic
Genetically Transmitted Systemic Diseases
Cystinosis
Lowe syndrome
Wilson syndrome
Fanconi-Bickel syndrome
Tyrosinemia
Galactosemia
Hereditary fructose intolerance (during fructose ingestion)
Metachromatic leukodystrophy
Pyruvate carboxylase deficiency
Methylmalonic acidemia
Dysproteinemic States
Multiple myeloma
Monoclonal gammopathy
Secondary Hyperparathyroidism with Chronic Hypocalcemia
Vitamin D deficiency or resistance
Vitamin D dependency
Drugs or Toxins
Ifosfamide
Cisplatin
Outdated tetracycline
3-Methylchromone
Streptozotocin
Valproate
Topiramate
Lead
Mercury
Amphotericin B (historical)
Tubulointerstitial Diseases
Sjögren syndrome
Medullary cystic disease
Renal transplantation
Other Renal and Miscellaneous Diseases
Nephrotic syndrome
Amyloidosis
Paroxysmal nocturnal hemoglobinuria

From DuBose TD Jr. Disorders of acid-base balance. In: Skorecki K, Chertow GM, Marsden PA, et al., eds. *Brenner & Rector's The Kidney,* 10th ed. Philadelphia: Elsevier; 2016: Table 17-7.

year of life with severe tubular dysfunction and growth failure. If the disease is not treated, the children develop end-stage kidney disease by the end of their first decade. A milder form of the disease manifests by adolescence called juvenile or intermediate nephropathic cystinosis, and it is characterized by less severe tubular abnormalities and a slower progression to renal failure. A nonnephropathic adult form also exists called ocular cystinosis and has isolated ocular involvement.

Cystinosis is caused by pathogenic variants in *CTNS,* which encodes the protein cystinosin, a lysosomal cystine transporter. Genotype-phenotype studies demonstrate that patients with severe nephropathic cystinosis carry variants that lead to complete loss of cystinosin function. Patients with milder clinical disease have variants that lead to the expression of partially functional protein. Patients with nephropathic cystinosis present with clinical manifestations reflecting their pronounced tubular dysfunction and Fanconi syndrome, including polyuria and polydipsia, growth failure, and rickets. Fever, caused by dehydration or diminished sweat production, is common. Patients are typically fair skinned and blond because of diminished pigmentation. Ocular presentations include photophobia, retinopathy, and impaired visual acuity. Patients also can develop hypothyroidism, hepatosplenomegaly, and delayed sexual maturation. With progressive tubulointerstitial fibrosis, CKD is invariant.

The diagnosis of cystinosis is suggested by the detection of cystine crystals in the cornea and confirmed by measurement of increased leukocyte cystine content and genetic testing for biallelic pathogenic variants in the *CTNS* gene. Prenatal testing is available for at-risk families.

Treatment of cystinosis is directed at correcting the metabolic abnormalities associated with Fanconi syndrome. In addition, lifelong therapy is required with cysteamine, a therapy which converts cystine to cysteine and a cysteine-cysteamine heterodimer. This facilitates lysosomal transport and decreases tissue cystine. Oral cysteamine does not achieve adequate levels in ocular tissues, so additional therapy with cysteamine eyedrops is required. Early initiation of cysteamine can prevent or delay deterioration of renal function and the need for renal replacement therapy. Patients with growth failure that does not improve with cysteamine may benefit from treatment with growth hormone. Kidney transplantation is a viable option in patients with renal failure. With prolonged survival, additional complications may become evident, including central nervous system abnormalities, muscle weakness, swallowing dysfunction, and pancreatic insufficiency. It is unclear whether long-term cysteamine therapy will decrease these complications.

Lowe Syndrome

Lowe syndrome (oculocerebrorenal syndrome of Lowe) is a rare X-linked disorder characterized by congenital cataracts, developmental delay, and Fanconi syndrome. The disease is caused by pathogenic variants in *OCRL1,* which encodes the phosphatidylinositol polyphosphate 5-phosphatase protein. The abnormalities seen in Lowe syndrome are thought to be caused by abnormal transport of vesicles within the Golgi apparatus. Kidneys show nonspecific tubulointerstitial changes. Thickening of glomerular basement membrane and changes in proximal tubule mitochondria are also seen.

Patients with Lowe syndrome typically present in infancy with cataracts, progressive growth failure, hypotonia, and Fanconi syndrome. Significant low molecular weight proteinuria is common. Blindness and CKD often develop. Characteristic behavioral abnormalities are also seen, including tantrums, stubbornness, stereotypy (repetitive behaviors), and obsessions. There is no specific therapy for the renal disease or neurologic deficits. Cataract removal is generally required.

569.2 Distal (Type I) Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

dRTA can be sporadic or inherited. It can also occur as a complication of inherited or acquired diseases of the distal tubules. Primary or secondary causes of dRTA can result from damaged or impaired

functioning of one or more transporters or proteins involved in the acidification process, including the H^+/ATPase, the HCO_3^-/Cl^- anion exchangers, or the components of the aldosterone pathway. Because of impaired hydrogen ion excretion, the urine pH cannot be reduced to <5.5, despite the presence of severe metabolic acidosis. Loss of sodium bicarbonate distally, due to lack of H^+ to bind to in the tubular lumen (see Fig. 569.1), results in increased chloride absorption and hyperchloremia. Inability to secrete H^+ is compensated for by increased K^+ secretion distally, leading to hypokalemia. **Hypercalciuria** is usually present and can lead to nephrocalcinosis or nephrolithiasis. Chronic metabolic acidosis also impairs urinary citrate excretion. **Hypocitraturia** further increases the risk of calcium deposition in the tubules. Bone disease is common, resulting from mobilization of organic components from bone to serve as buffers to chronic acidosis.

CLINICAL MANIFESTATIONS OF DISTAL RTA

dRTA shares features with those of pRTA, including non–anion gap metabolic acidosis and growth failure; distinguishing features of dRTA include nephrocalcinosis and hypercalciuria. The phosphate and massive bicarbonate wasting characteristic of pRTA is generally absent. Table 569.2 lists the causes of primary and secondary dRTA. Although inherited forms are rare, three specific inherited forms of dRTA have been identified, including an autosomal recessive form associated with sensorineural deafness.

Medullary sponge kidney is a relatively rare sporadic disorder in children, although not uncommon in adults. *HNF1B* pathogenic variants have been implicated in some patients. It is characterized by cystic dilation of the terminal portions of the collecting ducts as they enter the renal pyramids. On ultrasound studies, patients often have medullary nephrocalcinosis. Although patients with this condition typically maintain normal renal function through adulthood, complications include nephrolithiasis, pyelonephritis, hyposthenuria (inability to concentrate urine), and dRTA. Associations of medullary sponge kidney with Beckwith-Wiedemann syndrome or hemihypertrophy have been reported.

569.3 Hyperkalemic (Type IV) Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

Type IV RTA occurs as the result of impaired aldosterone production *(hypoaldosteronism)* or impaired renal responsiveness to aldosterone *(pseudohypoaldosteronism)*. Acidosis results because aldosterone has a direct effect on the H^+/ATPase responsible for hydrogen secretion. In addition, aldosterone is a potent stimulant for potassium secretion in the collecting tubule; consequently, lack of aldosterone results in hyperkalemia. This further affects the acid-base status by inhibiting ammoniagenesis and, thus, H^+ excretion. Aldosterone deficiency typically occurs as a result of adrenal gland disorders such as Addison disease or some forms of congenital adrenal hyperplasia. In children, aldosterone unresponsiveness is a more common cause of type IV RTA. This can occur transiently, during an episode of acute pyelonephritis or acute urinary obstruction, or chronically, particularly in infants and children with a history of obstructive uropathy. The latter patients can have significant hyperkalemia, even in instances when renal function is normal or only mildly impaired. Rare examples of inherited forms of type IV RTA have been identified (Table 569.3).

CLINICAL MANIFESTATIONS OF TYPE IV RTA

Patients with type IV RTA can present with growth failure in the first few years of life. Polyuria and dehydration (from salt wasting) are common. Rarely, patients (especially those with pseudohypoaldosteronism type 1) present with life-threatening hyperkalemia.

Table 569.2 Disorders with Dysfunction of Renal Acidification—Selective Defect in Net Acid Excretion: Classic Distal Renal Tubular Acidosis

PRIMARY DISORDERS
Familial
Autosomal dominant
SLC4A1 gene
Autosomal recessive
With deafness (*rdRTA1* or *ATP6V1B1* gene)
Without deafness (*rdRTA2* or *ATP6V0A4*)
Sporadic
ENDEMIC DISORDERS
Northeastern Thailand
DISORDERS SECONDARY TO SYSTEMIC DISORDERS
Autoimmune Diseases
Hyperglobulinemic purpura
Fibrosing alveolitis
Cryoglobulinemia
Chronic active hepatitis
Sjögren syndrome
Primary biliary cirrhosis
Thyroiditis
Polyarteritis nodosa
HIV nephropathy
Hypercalciuria and Nephrocalcinosis
Primary hyperparathyroidism
Hyperthyroidism
Medullary sponge kidney
Fabry disease
X-linked hypophosphatemia
Vitamin D intoxication
Idiopathic hypercalciuria
Wilson disease
Hereditary fructose intolerance
DRUG- AND TOXIN-INDUCED DISEASE
Amphotericin B
Toluene
Cyclamate
Mercury
Hepatic cirrhosis
Vanadate
Ifosfamide
Lithium
Foscarnet
Classic analgesic nephropathy
TUBULOINTERSTITIAL DISEASES
Balkan nephropathy
Kidney transplantation
Chronic pyelonephritis
Leprosy
Obstructive uropathy
Vesicoureteral reflux
Jejunoileal bypass with hyperoxaluria
DISORDERS ASSOCIATED WITH GENETICALLY TRANSMITTED DISEASES
Ehlers-Danlos syndrome
Hereditary elliptocytosis
Sickle cell anemia
Marfan syndrome
Medullary cystic disease
Hereditary sensorineural deafness
Jejunal bypass with hyperoxaluria
Osteopetrosis with carbonic anhydrase II deficiency (mixed proximal and distal RTA type III)
Carnitine palmitoyltransferase deficiency

From Hamm LL, DuBose TD Jr. Disorders of acid-base balance. In: Yu AS, Chertow GM, Luyckx VA, et. Al., eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Table 16.9.

Table 569.3 Disorders with Dysfunction of Renal Acidification: Generalized Abnormality of Distal Nephron with Hyperkalemia

MINERALOCORTICOID DEFICIENCY

Primary Mineralocorticoid Deficiency

- Combined deficiency of aldosterone, desoxycorticosterone, and cortisol
  - Addison disease
  - Bilateral adrenalectomy
  - Bilateral adrenal destruction
  - Hemorrhage or carcinoma
- Congenital enzymatic defects
  - 21-Hydroxylase deficiency
  - 3β-Hydroxydehydrogenase deficiency
  - Desmolase deficiency
- Isolated (selective) aldosterone deficiency
  - Chronic idiopathic hypoaldosteronism
  - Heparin (low molecular weight or unfractionated) administration in critically ill patient
  - Familial hypoaldosteronism
  - Corticosterone methyl oxidase deficiency types 1 and 2
  - Primary zona glomerulosa defect
  - Transient hypoaldosteronism of infancy
  - Persistent hypotension and/or hypoxemia
- Angiotensin-converting enzyme inhibition
  - Endogenous
  - Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Secondary Mineralocorticoid Deficiency

- Hyporeninemic hypoaldosteronism
  - Diabetic nephropathy
  - Tubulointerstitial nephropathies
  - Nephrosclerosis
  - Nonsteroidal antiinflammatory agents
  - Acquired immunodeficiency syndrome
  - Immunoglobulin M monoclonal gammopathy
  - Obstructive uropathy

MINERALOCORTICOID RESISTANCE

- PHA I: autosomal dominant (human mineralocorticoid receptor defect)

Renal Tubular Dysfunction (Voltage Defect)

- PHA I: autosomal recessive
- PHA II: autosomal dominant
- Drugs that interfere with Na^+ channel function in the CCT
  - Amiloride
  - Triamterene
  - Trimethoprim
  - Pentamidine
- Drugs that interfere with Na^+-K^+-ATPase in the CCT
  - Cyclosporine
  - Tacrolimus
- Drugs that inhibit aldosterone effect on the CCT
  - Spironolactone
  - Eplerenone
- Disorders associated with tubulointerstitial nephritis and renal insufficiency
  - Lupus nephritis
  - Methicillin nephrotoxicity
  - Obstructive nephropathy
  - Kidney transplant rejection
  - Sickle cell disease
  - Williams syndrome with uric acid nephrolithiasis

ATPase, Adenosine triphosphatase; CCT, cortical collecting tubule; PHA I, PHA II, pseudohypoaldosteronism types 1 and 2.

From Hamm LL, DuBose TD Jr. Disorders of acid-base balance. In: Yu AS, Chertow GM, Luyckx VA, et al., eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Table 16.11.

Patients with obstructive uropathies can present acutely with signs and symptoms of pyelonephritis, such as fever, vomiting, and foul-smelling urine. Laboratory tests reveal a hyperkalemic non–anion gap metabolic acidosis. Urine may be alkaline or acidic. Elevated urinary sodium levels with inappropriately low urinary potassium levels reflect the absence of aldosterone effect.

DIAGNOSTIC APPROACH TO RENAL TUBULAR ACIDOSIS

The first step in the evaluation of a patient with suspected RTA is to confirm the presence of a normal anion gap metabolic acidosis, identify electrolyte abnormalities, assess renal function, and rule out other causes of bicarbonate loss such as diarrhea (Table 569.4). Metabolic acidosis associated with diarrheal dehydration is extremely common, and acidosis generally improves with correction of volume depletion. Patients with protracted diarrhea can deplete their total-body bicarbonate stores and can have persistent acidosis despite apparent restoration of volume status. In instances where a patient has a recent history of severe diarrhea, full evaluation for RTA should be delayed for several days to permit adequate time for reconstitution of total-body bicarbonate stores. If acidosis persists beyond a few days in this setting, additional studies are indicated.

Serum electrolytes, BUN, calcium, phosphorus, creatinine, and venous blood gas for pH should be obtained by venipuncture. Traumatic blood draws (such as heel-stick specimens), small volumes of blood in adult-size specimen collection tubes, or a prolonged specimen transport time at room temperature can lead to falsely low bicarbonate levels, often in association with an elevated serum potassium value. True hyperkalemic acidosis is consistent with type IV RTA, whereas the finding of normal or low potassium suggests type I or II RTA. The **blood anion gap** should be calculated using the formula $[Na^+] - [Cl^- + HCO_3^-]$. Typically, values of <12 demonstrate the absence of an anion gap. Values of >20 indicate the presence of an anion gap and other diagnoses (lactic acidosis, diabetic ketoacidosis, inborn errors of metabolism, ingested toxins) should be investigated. If tachypnea is noted, evaluation of an arterial blood gas may be appropriate to evaluate the possibility of a mixed acid-base disorder primarily involving respiratory and metabolic components. A detailed history, with particular attention to growth and development, recent or recurrent diarrheal illnesses, a family history of developmental delay, failure to thrive, end-stage kidney disease, infant deaths, or miscarriages is essential. The physical examination should determine growth parameters and volume status as well as the presence of any dysmorphic features suggesting an underlying syndrome.

Once the presence of a non–anion gap metabolic acidosis is confirmed, the urine pH can help distinguish distal from proximal causes. A urine pH <5.5 in the presence of acidosis suggests pRTA, whereas patients with dRTA typically have a urine pH >6.0. The **urine anion gap** ([urine Na^+ + urine K^+] – urine Cl^-) is sometimes calculated to confirm the diagnosis of dRTA. A positive gap suggests a deficiency of ammoniagenesis and, thus, the possibility of a dRTA. A negative gap is consistent with proximal tubule bicarbonate wasting (or gastrointestinal bicarbonate wasting). A urinalysis should also be obtained to determine the presence of glycosuria, proteinuria, or hematuria, suggesting more global tubular damage or dysfunction. Random or 24-hour urine calcium and creatinine measurements will identify hypercalciuria. Renal ultrasonography should be performed to identify underlying structural abnormalities such as obstructive uropathies, as well as to determine the presence of nephrolithiasis or nephrocalcinosis (Fig. 569.2).

TREATMENT AND PROGNOSIS

The mainstay of therapy in all forms of RTA is bicarbonate replacement. Patients with pRTA often require large quantities of bicarbonate, up to 20 mEq/kg/24 hr, in the form of sodium bicarbonate or sodium citrate solution (Bicitra or Shohl solution). The base requirement for dRTA is generally in the range of 2-4 mEq/kg/24 hr, although individual patient requirements can vary. Patients with Fanconi syndrome usually require phosphate supplementation. Patients with dRTA should be monitored for the development of hypercalciuria. Those with symptomatic hypercalciuria (recurrent episodes of gross hematuria), nephrocalcinosis, or nephrolithiasis may require

Table 569.4 Contrasting Features and Diagnostic Studies in Renal Tubular Acidosis

	TYPE OF RENAL TUBULAR ACIDOSIS		
FINDING	**PROXIMAL**	**CLASSIC DISTAL**	**GENERALIZED DISTAL DYSFUNCTION**
Plasma [K^+]	Low	Low	High
Urine pH with acidosis	<5.5	>5.5	<5.5 or >5.5
Urine net charge	Negative	Positive	Positive
Fractional bicarbonate excretion	>10–15% during alkali therapy	2–5%	5–10%
U−BPco_2	Normal	Low	Low
Response to therapy	Least responsive	Responsive	Less responsive
Associated features	Fanconi syndrome	Nephrocalcinosis/ hyperglobulinemia	Renal insufficiency

U−BPco_2, urine minus blood CO_2 pressure.
Modified from DuBose TD Jr. Disorders of acid-base balance. In: Skorecki K, Chertow GM, Marsden PA, et al., eds. *Brenner & Rector's The Kidney,* 10th ed. Philadelphia: Elsevier; 2016: Table 17-17.

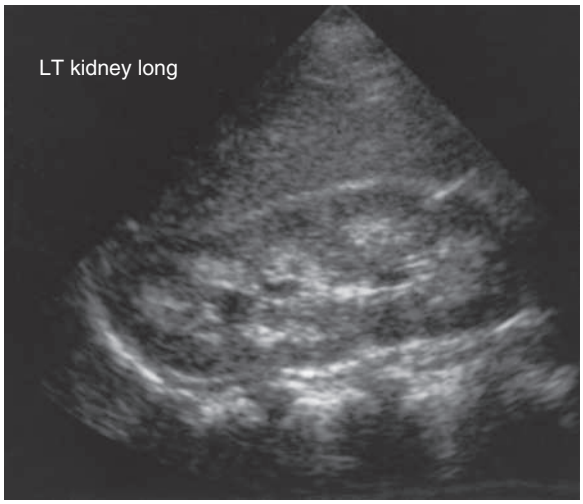

Fig. 569.2 Ultrasound examination of a child with distal RTA, demonstrating medullary nephrocalcinosis.

thiazide diuretics to decrease urine calcium excretion. Patients with type IV RTA can require chronic treatment for hyperkalemia with a sodium-potassium exchange resin (i.e., sodium polystyrene sulfonate or patiromer).

The prognosis of RTA depends to a large extent on the nature of any existing underlying disease. Patients with treated isolated proximal or dRTA generally demonstrate improvement in growth, provided serum bicarbonate levels can be maintained in the normal range. Patients with systemic illness and Fanconi syndrome can have ongoing morbidity with growth failure, rickets, and signs and symptoms related to their underlying disease.

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569.4 Rickets Associated with Renal Tubular Acidosis

Melisha G. Hanna and Bradley P. Dixon

Rickets may be present in primary RTA, *particularly in pRTA,* due to the added features of hypophosphatemia and phosphaturia from generalized proximal tubular dysfunction. Bone demineralization without overt rickets usually is detected in distal (type I) RTA. This metabolic bone disease may be characterized by bone pain, growth retardation, osteopenia, and, occasionally, pathologic fractures. Bone demineralization in dRTA probably relates to dissolution of bone because the calcium carbonate in bone serves as a buffer against the metabolic acidosis due to the hydrogen ions retained by patients with RTA.

Administration of sufficient bicarbonate to reverse acidosis reverses bone dissolution and the hypercalciuria that is common in dRTA. pRTA is treated with both bicarbonate and oral phosphate supplements to heal rickets. Doses of phosphate similar to those used in familial hypophosphatemia or Fanconi syndrome may be indicated. Vitamin D is required to offset the secondary hyperparathyroidism that complicates oral phosphate therapy. Following therapy, growth in patients with type II (proximal) RTA is greater than in patients with primary Fanconi syndrome.

Chapter 570 Nephrogenic Diabetes Insipidus

Margret E. Bock and Bradley P. Dixon

Nephrogenic diabetes insipidus (NDI) is a rare congenital or, more commonly, acquired, disorder of water metabolism characterized by an inability of the kidneys to concentrate urine, even in the presence of antidiuretic hormone (ADH). The most common pattern of inheritance in congenital NDI is as an X-linked recessive disorder (90% of cases of congenital NDI). Rarely, affected females are seen, presumably secondary to nonrandom X-chromosome inactivation. Approximately 10% of cases of congenital NDI are inherited as autosomal dominant or recessive disorders, with males and females affected equally. The clinical phenotype of autosomal recessive forms is similar to that of the X-linked form. Secondary (acquired) forms of NDI, either partial or complete, are not uncommon. They may be seen in many disorders affecting renal tubular function, including obstructive uropathies, acute kidney injury or chronic kidney disease, cystic kidney diseases, interstitial nephritis,

nephrocalcinosis, or toxic nephropathy caused by hypokalemia, hypercalcemia, lithium, or amphotericin B.

PATHOGENESIS

The ability to concentrate urine (and thus absorb water) requires three components: (1) the delivery of urine to the collecting tubule, (2) an intact concentrating gradient in the renal medulla, and (3) the ability to modulate water permeability in the collecting tubule by ADH. ADH (also called arginine vasopressin [AVP]) is synthesized in the hypothalamus and stored in the posterior pituitary. Under basal situations, the collecting tubule is impermeable to water. However, in response to increased serum osmolality (as detected by osmoreceptors in the hypothalamus) and/or severe volume depletion, ADH is released into the systemic circulation. It then binds to its receptor, vasopressin V2R (AVPR2), on the basolateral membrane of the collecting tubule cell. Binding of the hormone to its receptor activates a cyclic adenosine monophosphate–dependent cascade that results in insertion of preformed water channels (aquaporin 2 [AQP2]) into the luminal membrane of the collecting duct, rendering it permeable to water.

Pathogenic variants in *AVPR2* cause the more common X-linked form of NDI. Pathogenic variants in *AQP2* have been identified in patients with the rarer autosomal dominant and recessive forms. Pathogenic variants in *STIM1* (stromal interaction molecular 1) have also been identified in a mouse model exhibiting partial NDI, due to abnormalities in intracellular calcium regulation by the endoplasmic reticulum. Prenatal testing is available for families at risk for X-linked NDI. Patients with secondary forms of NDI can have ADH resistance due to defective aquaporin expression (as seen in lithium intoxication). Most often, secondary ADH resistance occurs as the result of loss of the hypertonic medullary gradient as a result of solute diuresis or tubular damage, resulting in the inability to absorb sodium or urea.

CLINICAL MANIFESTATIONS

Patients with congenital NDI typically present in the newborn period with massive polyuria, volume depletion, hypernatremia, and hyperthermia. Irritability and inconsolability are common features. Constipation and poor weight gain are also seen. After multiple episodes of **hypernatremic dehydration** in infancy, patients may develop intellectual disabilities, although this has become less common with cautious fluid resuscitation and gradual correction of hypernatremia. Toddlers and older children often display a marked thirst and a preference particularly for cold water. Mediated by the intact thirst mechanism, the need to consume large volumes of water during the day is profound, and patients often have diminished appetite and poor food intake, which may contribute to failure to thrive. However, even with adequate caloric supplementation, patients still exhibit growth abnormalities. Daytime and nighttime enuresis, caused by large urine volumes, is common. Patients with congenital NDI also may exhibit behavioral problems, including hyperactivity and short-term memory problems. Patients with the secondary form generally present later in life, primarily with hypernatremia and polyuria. Associated symptoms such as developmental delay and behavioral abnormalities are less common in this latter group.

DIAGNOSIS

The diagnosis is suggested in a male infant with polyuria, hypernatremia, and dilute urine. Simultaneous serum and urine osmolality measurements should be obtained. *If the serum osmolality value is ≥290 mOsm/kg with a simultaneous urine osmolality value of <290 mOsm/kg, a formal water-deprivation test is not necessary.* Because the differential diagnosis includes causes of **central diabetes insipidus,** the inability to respond to ADH (and thus the presence of NDI) should be confirmed by the administration of vasopressin (10-20 μg intranasally) followed by serial urine and serum osmolality measurements hourly for 4 hours. In patients with possible "partial" or secondary diabetes insipidus, in whom the initial serum osmolality value may be <290 mOsm/kg, a water-deprivation test should be considered. Fluids should be withheld and urine and serum osmolalities measured periodically until the serum osmolality value is >290 mOsm/kg; vasopressin is then given as before. Criteria for premature termination of a water-deprivation test include a decrease in body weight of >3%. These evaluations typically require an inpatient admission, given the need for serial laboratory monitoring and prompt intervention/response to results. If NDI is confirmed or suspected, an additional evaluation should include a detailed history to assess possible toxic exposures, determination of renal function by serum creatinine and BUN levels, and renal ultrasonography to identify obstructive uropathies or cystic kidney disease. Because of the massive urine output, patients with congenital NDI can have *nonobstructive hydronephrosis* of varying severity.

TREATMENT AND PROGNOSIS

Treatment of NDI includes maintenance of adequate fluid intake and access to free water, minimizing the urine output by limiting the solute load with a low-osmolar, low-sodium diet, and administering medications directed at decreasing the urine output. For infants, human milk or a low-solute formula, such as Similac PM 60/40, is preferred. Most infants with congenital NDI require gastrostomy or nasogastric feedings to ensure adequate fluid administration throughout the day and night. Sodium intake in older patients should be <0.7 mEq/kg/24 hr**.** Thiazide diuretics (2-3 mg/kg/24 hr of hydrochlorothiazide) effectively induce sodium loss and stimulate proximal tubule reabsorption of water. Potassium-sparing diuretics, in particular, amiloride (0.3 mg/kg/24 hr in three divided doses), are often additionally indicated. Patients who have an inadequate response to diuretics alone might benefit from the addition of prostaglandin synthetase inhibitors such as indomethacin (2 mg/kg/24 hr), which has an additive effect in reducing water excretion in some patients. Renal function must be monitored closely in such patients because indomethacin can cause deterioration in renal function over time. Patients with secondary NDI may not require medications but should have access to free water. Such patients should have the serum electrolytes and volume status monitored closely, particularly during periods of superimposed acute illnesses. Amiloride may also play a role in managing lithium-induced NDI by blocking entry of lithium into the tubular cell through the epithelial sodium channel (ENaC).

Prevention of recurrent dehydration and hypernatremia in patients with congenital NDI has significantly improved the neurodevelopmental outcome of these patients. However, behavioral issues remain a significant problem. In addition, chronic use of nonsteroidal antiinflammatory drugs can predispose patients to chronic kidney disease. The prognosis of patients with secondary NDI generally depends on the nature of the underlying disease.

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Chapter 571

Inherited Tubular Transport Abnormalities

571.1 Bartter Syndrome

Danielle E. Soranno and Bradley P. Dixon

Bartter syndrome is a group of disorders characterized by hypokalemic hypochloremic metabolic alkalosis with hypercalciuria and salt wasting (see Chapter 73). These disorders are currently classified by the anatomic site affected by the pathogenic variant (Tables 571.1 and 571.2). **Antenatal Bartter syndrome** (types I, II, and IV; also called hyperprostaglandin E syndrome) typically manifests in infancy and has a more severe phenotype than **classic Bartter syndrome** (type III). The perinatal onset includes maternal polyhydramnios, neonatal salt wasting, and severe episodes of recurrent dehydration. The milder phenotype, classic Bartter syndrome, manifests in childhood with failure to thrive and a history of recurrent episodes of dehydration. A phenotypically related disease, **Gitelman syndrome**, has a distinct genetic defect and is discussed in Chapter 571.2 (see Table 571.1). One distinct variant of antenatal Bartter syndrome is associated with sensorineural deafness (type IV). Bartter-like phenotypes have been noted in other diseases such as Kearns-Sayre syndrome.

PATHOGENESIS

The biochemical features of Bartter syndrome, such as hypokalemic hypochloremic metabolic alkalosis with hypercalciuria, resemble those seen with chronic use of loop diuretics and reflect a defect in sodium, chloride, and potassium transport in the ascending loop of Henle. The urinary loss of sodium and chloride, with resultant volume contraction, stimulates the renin-angiotensin II-aldosterone axis. Aldosterone promotes distal sodium uptake and potassium secretion, exacerbating the hypokalemia. It also stimulates hydrogen ion secretion distally, worsening the metabolic alkalosis. Hypokalemia stimulates prostaglandin synthesis, which further activates the renin-angiotensin II-aldosterone axis. Bartter syndrome has been associated with at least five distinct genetic defects in transporters along the loop of Henle (see Table 571.1). Each contributes, in some manner, to sodium and chloride transport. Pathogenic variants in the genes that encode the $Na^+/K^+/2Cl^-$ transporter (NKCC2, the site of action of furosemide), the luminal potassium channel (ROMK), combined chloride channel (CLC-Ka, CLC-Kb), or subunit of chloride channels (barttin) cause neonatal Bartter syndrome. Isolated defects in the genes that produce a specific basolateral chloride channel (ClC-Kb) cause classic Bartter syndrome.

CLINICAL MANIFESTATIONS

A history of maternal polyhydramnios with or without prematurity may be elicited. Dysmorphic features, including triangular facies, protruding ears, large eyes with strabismus, and drooping mouth may be present on physical examination. Consanguinity suggests the presence of an autosomal recessive disorder. Older children can have a history of recurrent episodes of polyuria with dehydration, failure to thrive, nonspecific fatigue, dizziness, and chronic constipation. Older children may also present with muscle cramps and weakness secondary

Table 571.1 Types of Bartter Syndrome, Gitelman Syndrome, and Related Conditions

DISORDER	OMIM, GENE	GENE PRODUCT	INHERITANCE	FEATURES
BS VARIANTS				
BS I (ABS, HPES)	601678, *SLC12A1*	NKCC2	AR	Polyhydramnios, prematurity, hypokalemic hypochloremic alkalosis, nephrocalcinosis, with or without concentrating defect
BS II (ABS with transient hyperkalemia and acidosis, HPES)	241200, *KCNJ1*	ROMK1	AR	Polyhydramnios, prematurity, transient hyperkalemia and acidosis, then hypokalemic hypochloremic alkalosis, nephrocalcinosis, with or without concentrating defect
BS III (CBS)	607364, *CLCNKB*	ClC-Kb	AR; many sporadic	Variable age at presentation with severity corresponding to type of gene pathogenic variant; hypokalemic hypochloremic alkalosis
BS IVa and BS IVb (ABS or HPES with sensorineural deafness)	602522, *BSND CLCNKA, CLCNKB*	Bartter ClC-Ka and ClC-Kb	AR	Polyhydramnios, prematurity, hypokalemic hypochloremic alkalosis, sensorineural deafness, with or without concentrating defect
BS V (transient ABS)	300971, *MAGED2*	MAGED2	XR	Severe polyhydramnios, hypokalemic hypochloremic alkalosis with symptoms resolving within the first few months of life
AD hypocalcemic hypercalciuria	601199, *L125P*	CaSR	AD	Hypocalcemic hypocalciuria, hypokalemic hypochloremic alkalosis, suppressed PTH
GS VARIANTS				
GS	263800, *SLC12A3*	NCC	AR	Present in later childhood or adulthood with weakness, lethargy, carpopedal spasm, hypokalemic alkalosis, hypomagnesemia, hypermagnesuria and hypocalciuria
EAST syndrome (SeSAME)	612780, *Kir4.1*	KCNJ10	AR	Epilepsy, ataxia, sensorineural deafness, hypokalemic hypochloremic alkalosis
OTHER VARIANTS				
CLDN10 pathogenic variants	617579, *CLDN10*	Claudin-10	AR	Hypokalemic metabolic alkalosis with hypocalciuria but normal to elevated magnesium

ABS, Antenatal Bartter syndrome; AD, autosomal dominant; AR, autosomal recessive; BS, Bartter syndrome; CaSR, calcium-sensing receptor; CBS, classic Bartter syndrome; ClC-Ka, chloride channel-Ka; ClC-Kb, chloride channel-Kb; GS, Gitelman syndrome; HPES, hyperprostaglandin E syndrome; MAGED, melanoma-associated antigen-D2; NCC, thiazide-sensitive NaCl cotransporter; NKCC2, furosemide-sensitive Na-K-2Cl cotransporter; OMIM, Online Mendelian Inheritance in Man; PTH, parathyroid hormone; ROMK, renal outer medullary K channel; SeSAME, seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalances; XR, X-linked recessive.
From Fulchiero R, Seo-Mayer P. Bartter syndrome and Gitelman syndrome. *Pediatr Clin North Am*. 2019;66:121–134. Box 1.

Table 571.2 Features That Distinguish Bartter and Gitelman Syndrome Variants

VARIANT	AGE OF ONSET	SERUM K	SERUM CL	SERUM MG	SERUM RENIN, ALDOSTERONE	URINE CA/CR	OTHER DISTINCT FEATURES
BS I	AN	Low	Low	Normal	High, high	High	—
BS II	AN	High, then low	Low	Normal	High, high	High	Transient hyperkalemia
BS III	N, C, A	Low	Very low	Normal	High, high	Low, normal, or high	—
BS IVa, IVb	AN	Low	Low	Normal	High, high	Normal or high	Sensorineural deafness
BS V	AN	Low	Low	Normal	High, high	—	Transient features
Hypocalcemic hypercalciuria	—	Low	Low	Normal	High, high	High	Family history, hypocalcemia, suppressed PTH
GS	C, A	Low	Low	Low	High, high	Low	—
EAST syndrome	—	Low	Low	Low	High, high	Low	Epilepsy, ataxia, sensorineural deafness

A, Adult; AN, antenatal; BS, Bartter syndrome; C, child; Ca/Cr, spot calcium to creatinine ratio; GS, Gitelman syndrome; Mg, magnesium; N, neonate; PTH, parathyroid hormone.
From Fulchiero R, Seo-Mayer P. Bartter syndrome and Gitelman syndrome. *Pediatr Clin North Am*. 2019;66:121–134. Box 3.

to chronic hypokalemia. Blood pressure is usually preserved, although patients with the antenatal form can have severe salt wasting, resulting in dehydration and hypotension. Serum chemistry reveals the classic biochemical abnormalities of a **hypokalemic hypochloremic metabolic alkalosis.** Renal function is typically normal. Urinary calcium levels are typically elevated, as are urinary potassium and sodium levels. Serum renin, aldosterone, and prostaglandin E levels are often markedly elevated, particularly in the more severe antenatal form. Nephrocalcinosis, resulting from hypercalciuria, may be seen on ultrasound examination (types I and II).

DIAGNOSIS

The diagnosis is usually made based on the clinical presentation and laboratory findings. The diagnosis in the neonate or infant is suggested by severe hypokalemia, usually <2.5 mmol/L, with metabolic alkalosis. Hypercalciuria is typical; hypomagnesemia is seen in a minority of patients but is more common in Gitelman syndrome. Because features of Bartter syndrome resemble the chronic use of loop diuretics, diuretic abuse should be considered in the differential diagnosis, even in young children. Chronic vomiting and cystic fibrosis can also present a similar clinical picture but can be distinguished by the measurement of **urinary chloride,** which is elevated in Bartter syndrome and low in patients with chronic vomiting and cystic fibrosis. Kidneys demonstrate hyperplasia of the juxtaglomerular apparatus, although renal biopsy is rarely performed to diagnose this condition.

TREATMENT AND PROGNOSIS

Treatment of Bartter syndrome is directed at preventing dehydration, maintaining nutritional status, and correcting hypokalemia. Potassium supplementation, usually in the form of potassium chloride to correct the concomitant chloride depletion and often at very high doses, is required. Potassium-sparing diuretics (such as spironolactone) are also often used to inhibit distal potassium secretion. Even with appropriate therapy, serum potassium values might not normalize, particularly in patients with the neonatal form. Infants and young children require a high-sodium diet and, at times, sodium supplementation. Indomethacin, a prostaglandin inhibitor, can also be effective. If hypomagnesemia is present, magnesium supplementation is required. With close attention to electrolyte balance, volume status, and growth, the long-term prognosis is generally good. Routine monitoring is necessary, particularly during periods of growth, to ensure that electrolytes are maintained in a safe range. Strict return/call precautions are needed in times of illness with extrarenal volume loss such as vomiting or diarrhea. In a minority of patients, chronic hypokalemia, nephrocalcinosis, and chronic indomethacin therapy can lead to chronic interstitial nephritis and chronic renal failure.

571.2 Gitelman Syndrome

Danielle E. Soranno and Bradley P. Dixon

Gitelman syndrome (often called a *Bartter syndrome variant*) is a rare autosomal recessive cause of hypokalemic hypochloremic metabolic alkalosis, with distinct features of **hypocalciuria** and **hypomagnesemia.** Patients with Gitelman syndrome are typically diagnosed incidentally in late childhood or early adulthood (see Tables 571.1 and 571.2).

PATHOGENESIS

The biochemical features of Gitelman syndrome resemble those of chronic use of thiazide diuretics. Thiazides act on the sodium chloride cotransporter NCCT, present in the distal convoluted tubule. Through linkage analysis and mutational studies, defects in the gene encoding NCCT have been demonstrated in patients with Gitelman syndrome.

CLINICAL MANIFESTATIONS

Patients with Gitelman syndrome typically present at a later age than those with Bartter syndrome and may have symptoms similar to older children with Bartter syndrome (see Chapter 571.1). Patients often have a history of salt craving, recurrent muscle cramps and spasms, presumably caused by low serum magnesium levels, nocturia, polyuria, and occasional hypotension. They usually do not have a history of recurrent episodes of dehydration. Biochemical abnormalities include hypokalemia, metabolic alkalosis, and hypomagnesemia. The urinary calcium level is usually very low (in contrast to the elevated urinary calcium level often seen in Bartter syndrome), and the urinary magnesium level is elevated. Renin and aldosterone levels are usually normal, and prostaglandin E secretion is not elevated. Growth failure is less prominent in Gitelman syndrome than in Bartter syndrome.

DIAGNOSIS

The diagnosis of Gitelman syndrome is suggested in an adolescent or adult presenting with hypokalemic hypochloremic metabolic alkalosis, hypomagnesemia, and hypocalciuria. The diagnosis is often made incidentally after hypokalemia is noted on bloodwork, spurring further evaluation.

TREATMENT

Therapy is directed at correcting hypokalemia and hypomagnesemia with supplemental potassium and magnesium. Sodium supplementation or treatment with prostaglandin inhibitors is generally not necessary because patients typically do not have episodes of volume

depletion or elevated prostaglandin E excretion. Recently, SGLT2 inhibitors have begun to be utilized in adults with refractory hypomagnesemia; however, further studies are needed to investigate their utility in the treatment of Gitelman syndrome.

571.3 Other Inherited Tubular Transport Abnormalities

Danielle E. Soranno and Bradley P. Dixon

Inherited abnormalities in distinct transporters in each segment of the nephron have now been identified and the molecular defects have been characterized. Renal tubular acidosis and nephrogenic diabetes insipidus are discussed in detail in Chapters 569 and 570, respectively. **Cystinuria** is an autosomal recessive disorder seen primarily in patients of Middle Eastern descent and is characterized by recurrent stone formation. The disease is caused by a defective high-affinity transporter for L-cystine and dibasic amino acids present in the proximal tubule; affected females form fewer stones than males. Treatment focuses on stone prevention via hydration, sodium restriction, urine alkalinization, and cystine-binding therapy.

Dent disease is an X-linked proximal tubulopathy with characteristic abnormalities that include low molecular weight proteinuria, hypercalciuria, and variably other features of Fanconi syndrome, such as glycosuria, aminoaciduria, and phosphaturia. Although some patients develop nephrocalcinosis, nephrolithiasis, progressive renal failure, and hypophosphatemic rickets, patients with Dent disease typically do not have proximal renal tubular acidosis or extrarenal manifestations. Loss-of-function pathogenic variants of *CLCN5,* which encodes a renal Cl^-/H^+ antiporter (ClC-5), are reported in ~50–60% of patients with Dent disease. The genetic heterogeneity of Dent disease in some patients who exhibit pathogenic variants in the gene for OCRL1 (responsible for Lowe syndrome) also meet the criteria for Dent disease (~15% of patients) called Dent 2 disease. Dent disease includes X-linked recessive nephrolithiasis with renal failure, X-linked recessive hypophosphatemic rickets, and idiopathic low molecular weight proteinuria seen in Japanese children.

Pathogenic variants in an extracellular basolateral calcium-sensing receptor, normally present in the loop of Henle, can cause a **dominant Bartter syndrome–like picture** (also known as Bartter syndrome type V). These patients' predominant symptoms are hypocalcemia and suppressed parathyroid hormone function, which differentiates them from patients with Bartter syndrome.

In the distal convoluted tubule, gain-of-function pathogenic variants in *WNK1* and loss-of-function pathogenic variants in *WNK4,* both serine threonine kinases, lead to excessive NCCT-mediated salt reabsorption with the clinical picture of pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension, or **Gordon syndrome**), including volume expansion with hypertension, hyperkalemia, hyperchloremic metabolic acidosis, and hypercalciuria. Due to the excessive activation of the thiazide-sensitive NCCT, this disorder can be effectively treated with thiazide diuretics.

In the collecting duct, gain-of-function pathogenic variants of the gene that encodes the epithelial sodium channel (ENaC) cause an inherited form of hypertension, **Liddle syndrome.** Patients with this disorder have constitutive sodium uptake in the collecting duct, with hypokalemia and suppressed aldosterone. Due to the excessive activation of ENaC, potassium-sparing diuretics (specifically amiloride) are an effective treatment for Liddle syndrome. Conversely, loss-of-function pathogenic variants cause **pseudohypoaldosteronism,** characterized by severe sodium wasting and hyperkalemia as well as a distal (type IV) RTA (also discussed in Chapter 569.3). A variant of the latter disorder is associated with systemic abnormalities, including defects in sweat chloride, and can resemble cystic fibrosis.

Renal hypouricemia, a defect in *SLC22A12,* presents with low serum uric acid levels and is complicated by exercise-induced acute kidney injury. Patients have elevated urine uric acid levels and present with loin pain, nausea, and vomiting after exercise. Treatment is for acute kidney injury and reducing the intensity of exercise.

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Chapter 572 Renal Failure

572.1 Acute Kidney Injury

Prasad Devarajan

Acute kidney injury (AKI) has been traditionally defined as an abrupt loss of kidney function leading to a rapid decline in the glomerular filtration rate (GFR), accumulation of waste products such as blood urea nitrogen (BUN) and creatinine, and dysregulation of extracellular volume and electrolyte homeostasis. The term AKI has replaced acute renal failure (ARF); AKI embodies a continuum of renal dysfunction that ranges from a small increase in serum creatinine to complete anuric renal failure. The incidence of AKI varies from 5–10% of all hospitalizations to >25% in critically ill infants and children. The etiology of AKI varies widely according to age, geographic region, and clinical setting. Functional AKI induced by dehydration is usually reversible with early fluid therapy. However, the prognosis for patients with structural AKI in the intensive care setting with multiorgan failure remains guarded.

A classification system proposed by the Kidney Disease Improving Global Outcomes (KDIGO) AKI Consensus Conference takes both serum creatinine and urine output criteria into account to define and stage AKI (Table 572.1). Thus AKI is defined as

Increase in serum creatinine by ≥0.3 mg/dL from baseline within 48 hours, *or*

Increase in serum creatinine to ≥1.5 times baseline within the prior 7 days, *or*

Urine volume ≤0.5 mL/kg/hr for 6 hours

PATHOGENESIS

AKI has been conventionally classified into three categories: prerenal, intrinsic renal, and postrenal (Table 572.2 and Fig. 572.1).

Prerenal AKI, also called *prerenal azotemia,* is characterized by a diminished effective circulating arterial volume, which leads to inadequate kidney perfusion and a decreased GFR. Evidence of structural kidney damage is largely absent. Common causes of prerenal AKI include dehydration, sepsis, hemorrhage, severe hypoalbuminemia, and cardiac failure. If the underlying cause of the kidney hypoperfusion is reversed promptly, kidney function returns to normal. If hypoperfusion is sustained, intrinsic kidney parenchymal damage can develop.

Intrinsic renal AKI includes a variety of disorders characterized by kidney parenchymal damage, including sustained hypoperfusion and ischemia. Ischemic/hypoxic injury and nephrotoxic insults are the most common causes of intrinsic AKI in high-resource countries and are more common with an underlying comorbid condition; most are associated with cardiac, oncologic, urologic, kidney, and genetic disorders or prematurity (Table 572.3). Many forms of **glomerulonephritis,**

Table 572.1 Kidney Disease Improving Global Outcomes Staging of Acute Kidney Injury

STAGE	SERUM CREATININE	URINE OUTPUT
1	1.5-1.9 times baseline, OR ≥0.3 mg/dL increase	<0.5 mL/kg/hr for 6-12 hr
2	2.0-2.9 times baseline	<0.5 mL/kg/hr for ≥12 hr
3	3.0 times baseline, OR SCr ≥4.0 mg/dL, OR Initiation of renal replacement therapy, OR eGFR <35 mL/min per 1.73 m^2 (<18 yr)	<0.3 mL/kg/hr for ≥24 hr, OR Anuria for ≥12 hr

SCr, Serum creatinine; eGFR, estimated glomerular filtration rate.

Table 572.2 Common Causes of Acute Kidney Injury

PRERENAL
Dehydration (hypovolemia)
Gastroenteritis (hypovolemia)
Hemorrhage (hypovolemia)
Burns
Sepsis
Shock
Capillary leak/systemic inflammatory response syndrome
Hypoalbuminemia
Cirrhosis
Abdominal compartment syndrome
Cardiac failure
Anaphylaxis
INTRINSIC RENAL
Glomerulonephritis
Postinfectious/poststreptococcal
Lupus erythematosus
IgA vasculitis
Membranoproliferative
Anti–glomerular basement membrane
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
Acute tubular necrosis
Cortical necrosis
Renal vein thrombosis
Infarction
Rhabdomyolysis
Acute interstitial nephritis
Tumor infiltration
Toxin and drugs (see Table 572.3)
Tumor lysis syndrome
Vasculitis
POSTRENAL
Posterior urethral valves
Ureteropelvic junction obstruction
Ureterovesical junction obstruction
Ureterocele
Tumors
Urolithiasis
Urethral strictures
Hemorrhagic cystitis (blood clots)
Neurogenic bladder
Anticholinergic drugs

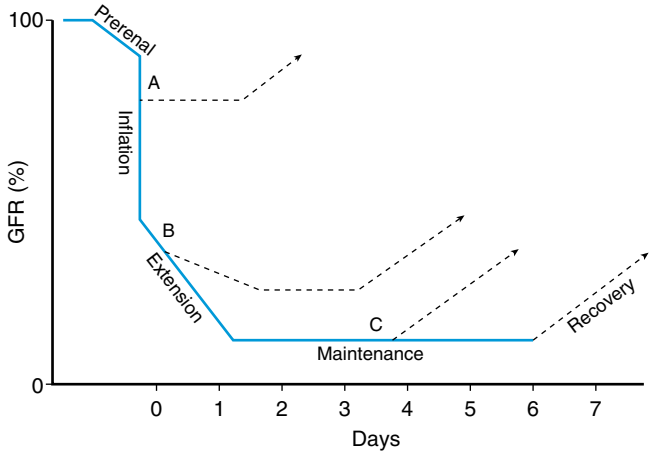

Fig. 572.1 Phases of acute kidney injury. GFR, Glomerular filtration rate. *(From Sutton TA, Fisher CJ, Molitoris BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. Kidney Int. 2002;62:1539–1549.)*

Table 572.3 Major Endogenous and Exogenous Toxins Causing Acute Tubular Injury

ENDOGENOUS TOXINS	EXOGENOUS TOXINS
MYOGLOBULINURIA	**ANTIBIOTICS**
Muscle breakdown: trauma, compression, electric shock, hypothermia, hyperthermia, seizures, exercise, burns	Aminoglycosides
Metabolic: hypokalemia, hypophosphatemia	Amphotericin B
Infections: tetanus, influenza	Antiviral agents: acyclovir, cidofovir, indinavir, foscarnet, tenofovir
Toxins: isopropyl alcohol, ethanol, ethylene glycol, toluene, snake and insect bites, cocaine, heroin	Pentamidine
Drugs: HMG-CoA reductase inhibitors (statins), amphetamines, fibrates	Piperacillin tazobactam**
Inherited disease: deficiency of myophosphorylase, phosphofructokinase, carnitine palmitoyltransferase	Vancomycin
Autoimmune: polymyositis, dermatomyositis	**CHEMOTHERAPY**
	Cisplatin
	CAR-T cell therapy*
	Ifosfamide
	Plicamycin
	5-Fluorouracil
	Cytarabine
	6-Thioguanine
	Methotrexate
	Immune checkpoint inhibitors
	CALCINEURIN INHIBITORS
	Cyclosporine
	Tacrolimus
HEMOGLOBINURIA	**ORGANIC SOLVENTS**
Mechanical: prosthetic valves, microangiopathic hemolytic anemia, extracorporeal circulation	Toluene
Drugs: hydralazine, methyldopa	Ethylene glycol
Chemicals: benzene, arsine, fava beans, glycerol, phenol	Mannitol
Immunologic: transfusion reaction	**POISONS**
Genetic: G6PD deficiency, PNH	Snake venom
	Paraquat
	MISCELLANEOUS
	Radiocontrast media
	Intravenous immune globulin
	ACE inhibitors
	Nonsteroidal antiinflammatory drugs
	Allopurinol
	Oral phosphate bowel preparations
	Synthetic cannabinoids
INTRATUBULAR OBSTRUCTION FROM CRYSTALLURIA OR PARAPROTEINS	
Tumor lysis syndrome	
HGPRT deficiency	
Multiple myeloma	
Oxalate (ethylene glycol)	

*Associated cytokine release syndrome, tumor lysis syndrome.
**Controversial
ACE, Angiotensin-converting enzyme; CAR-T, chimeric antigen receptor T cells; G6PD, glucose-6-phosphate dehydrogenase; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; PNH, paroxysmal nocturnal hemoglobinuria.
Modified from Weisbord SD, Palevsky PM. Acute kidney injury. In: Yu AS, Chertow GM, Luyckx VA, et al, eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Table 29.3.

including postinfectious glomerulonephritis, lupus nephritis, IgA vasculitis nephritis (formerly Henoch-Schönlein purpura nephritis), membranoproliferative glomerulonephritis, and anti–glomerular basement membrane nephritis, can also cause intrinsic AKI. Severe and prolonged ischemic/hypoxic injury and nephrotoxic insult lead to **acute tubular**

necrosis (ATN), seen most often in critically ill infants and children. Mechanisms leading to ischemic AKI include hypotension/intravascular volume depletion (hemorrhage, third-space fluid losses, diarrhea), decreased effective intravascular volume (heart failure, cirrhosis, hepatorenal syndrome, peritonitis, abdominal compartment syndrome), vasodilation/vasoconstriction (sepsis, hepatorenal syndrome), renal artery obstruction (thrombosis, embolization, stenosis), intrarenal artery disease (vasculitis, hemolytic uremic syndrome [HUS], sickle cell anemia, transplant rejection), and impaired renal blood flow (cyclosporine, tacrolimus, angiotensin-converting enzyme [ACE] inhibitors, angiotensin-receptor blocking agents, radiocontrast agents).

The typical pathologic feature of ATN is tubular cell necrosis, although significant histologic changes are not consistently seen in patients with clinical ATN. The mechanisms of injury in ATN can include alterations in intrarenal hemodynamics, tubular obstruction, and passive back leak of the glomerular filtrate across injured tubular cells into the peritubular capillaries.

Tumor lysis syndrome is a specific form of AKI related to spontaneous or chemotherapy-induced cell lysis in patients with lymphoproliferative malignancies. This disorder is primarily caused by obstruction of the tubules by uric acid crystals (see Chapters 544 and 545). **Acute interstitial nephritis** is another common cause of AKI and is usually a result of a hypersensitivity reaction to a therapeutic agent or various infectious agents (see Chapter 561.2).

Postrenal AKI includes a variety of disorders characterized by obstruction of the urinary tract. In neonates and infants, congenital conditions, such as posterior urethral valves and bilateral ureteropelvic junction obstruction, account for most cases of AKI. Other conditions, such as urolithiasis, tumor (intraabdominal lesion or within the urinary tract), hemorrhagic cystitis, and neurogenic bladder, can cause AKI in older children and adolescents. In a patient with two functioning kidneys, obstruction must be bilateral to result in AKI. Relief of the obstruction usually results in recovery of renal function, except in patients with associated renal dysplasia or prolonged urinary tract obstruction.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A carefully taken history is critical in defining the cause of AKI. An infant with a three day history of vomiting and diarrhea most likely has prerenal AKI caused by volume depletion, but hemolytic-uremic syndrome (HUS) must also be a consideration. A 6-year-old child with a recent pharyngitis who presents with periorbital edema, hypertension, and gross hematuria most likely has intrinsic AKI related to acute postinfectious glomerulonephritis. A critically ill child with a history of protracted hypotension or with exposure to nephrotoxic medications most likely has ATN. A neonate with a history of hydronephrosis seen on prenatal ultrasound studies and a palpable bladder most likely has congenital urinary tract obstruction, probably related to posterior urethral valves.

The physical examination must be thorough, with careful attention to volume status. Tachycardia, dry mucous membranes, and poor peripheral perfusion suggest an inadequate circulating volume and the possibility of prerenal AKI. Hypertension, peripheral edema, rales, and a cardiac gallop suggest volume overload and the possibility of intrinsic AKI from glomerulonephritis or ATN. The presence of a rash and arthritis might indicate systemic lupus erythematosus (SLE) or IgA vasculitis nephritis. Palpable flank masses may be seen with renal vein thrombosis, tumors, cystic disease, or urinary tract obstruction.

LABORATORY FINDINGS

Laboratory abnormalities can include anemia (the anemia is usually dilutional or hemolytic, as in SLE, renal vein thrombosis, HUS); leukopenia (SLE, sepsis); thrombocytopenia (SLE, renal vein thrombosis, sepsis, HUS); hyponatremia (dilutional); metabolic acidosis; elevated serum concentrations of blood urea nitrogen (BUN), creatinine, uric acid, potassium, and phosphate (diminished kidney function); and hypocalcemia (hyperphosphatemia).

The serum C3 level may be depressed (postinfectious glomerulonephritis, SLE, or membranoproliferative glomerulonephritis), and antibodies may be detected in the serum to streptococcal (poststreptococcal glomerulonephritis), nuclear (SLE), neutrophil cytoplasmic (granulomatosis with polyangiitis, microscopic polyarteritis), or glomerular basement membrane (Goodpasture disease) antigens.

The presence of hematuria, proteinuria, and red blood cell or granular urinary casts suggests intrinsic AKI, in particular glomerular disease and ATN. The presence of white blood cells and white blood cell casts with low-grade hematuria and proteinuria suggests tubulointerstitial disease. Urinary eosinophils may be present in some children with drug-induced tubulointerstitial nephritis.

Urinary indices may be useful in differentiating prerenal AKI from intrinsic AKI (Table 572.4). Patients whose urine shows an elevated specific gravity (>1.020), elevated urine osmolality (UOsm >500 mOsm/kg), low urine sodium (UNa <20 mEq/L), and fractional excretion of sodium <1% (<2.5% in neonates) most likely have prerenal AKI. Those with a specific gravity of <1.010, low urine osmolality (UOsm <350 mOsm/kg), high urine sodium (UNa >40 mEq/L), and fractional excretion of sodium >2% (>10% in neonates) most likely have intrinsic AKI.

Table 572.4 Urinalysis, Urine Chemistries, and Osmolality in Acute Kidney Injury

	HYPOVOLEMIA	ACUTE TUBULAR NECROSIS	ACUTE INTERSTITIAL NEPHRITIS	GLOMERULONEPHRITIS	OBSTRUCTION
Sediment	Bland, may have hyaline casts	Broad, brownish granular casts	White blood cells, eosinophils, cellular casts	Red blood cells, red blood cell casts	Bland or bloody
Protein	None or low	None or low	Minimal but may be increased with NSAIDs	Increased, >100 mg/dL	Low
Urine sodium (mEq/L)*	<20	>40	>30	<20	<20 (acute) >40 (few days)
Urine osmolality (mOsm/kg)	>400	<350	<350	>400	<350
Fractional excretion of sodium %†	<1	>2‡	Varies	<1	<1 (acute) >1 (few days)

*The sensitivity and specificity of urine sodium of <20 mEq/L in differentiating prerenal azotemia from acute tubular necrosis are 90% and 82%, respectively.
†Fractional excretion of sodium is the urine:plasma (U:P) ratio of sodium divided by U:P of creatinine × 100. The sensitivity and specificity of fractional excretion of sodium of <1% in differentiating prerenal azotemia from acute tubular necrosis are 96% and 95%, respectively.
‡The fractional excretion of sodium may be <1% in acute tubular necrosis secondary to radiocontrast material or rhabdomyolysis.
NSAIDs, Nonsteroidal antiinflammatory drugs.
From Singri N, Ahya SN, Levin ML. Acute renal failure. *JAMA*. 2003;289:747–751.

Chest radiography may reveal cardiomegaly, pulmonary congestion (fluid overload), or pleural effusions. Renal ultrasonography can reveal hydronephrosis and/or hydroureter, which suggest urinary tract obstruction, or nephromegaly, consistent with intrinsic renal disease. Renal biopsy may ultimately be required to determine the precise cause of AKI in patients who do not have clearly defined prerenal or postrenal AKI.

Although serum creatinine is used to measure kidney function, it is an insensitive and delayed measure of decreased kidney function following AKI. Tissue inhibitor of metallopritinase-2 (TIMP2) and insulin-like growth factor binding protein-7 (IGFBP7) are biomarkers for early tubular injury and the risk for the development of AKI used mostly in critically ill adult patients.

TREATMENT

Medical Management

Complications of AKI are noted in Table 572.5. In infants and children with urinary tract obstruction, such as in a newborn with suspected posterior ureteral valves, a bladder catheter should be placed immediately to ensure adequate drainage of the urinary tract. The placement of a bladder catheter may also be considered in nonambulatory older children and adolescents to accurately monitor urine output during AKI; however, precautions to prevent iatrogenic infection should be taken.

Determination of the volume status is of critical importance when initially evaluating a patient with AKI. If there is no evidence of volume overload or cardiac failure, the intravascular volume should be expanded by intravenous (IV) administration of isotonic saline, 20 mL/kg over 30 minutes. In the absence of blood loss or hypoproteinemia, colloid-containing solutions are not required for volume expansion. Severe hypovolemia may require additional fluid boluses (see Chapters 74, 75, and 85). Determination of the central venous pressure may be helpful if adequacy of the blood volume is difficult to determine. After volume resuscitation, hypovolemic patients generally void within 2 hours; failure to do so suggests intrinsic or postrenal AKI. Hypotension caused by sepsis requires vigorous fluid resuscitation followed by a continuous infusion of vasopressors.

Diuretic therapy should be considered only after the adequacy of the circulating blood volume has been established. Furosemide (2-4 mg/kg) may be administered as a single IV dose. Bumetanide (0.1 mg/kg) may be given as an alternative to furosemide. If urine output is not improved, then a continuous diuretic infusion may be considered. To increase renal cortical blood flow, many clinicians administer dopamine (2-3 μg/kg/min) in conjunction with diuretic therapy, although no controlled data support this practice. *There is little evidence that diuretics or dopamine can prevent AKI or hasten recovery*. Mannitol may be effective in the prevention of pigment (myoglobin, hemoglobin)-induced renal failure. Atrial natriuretic peptide may be of value in preventing or treating AKI, although there is little pediatric evidence to support its use.

If there is no response to a diuretic challenge, diuretics should be discontinued and fluid restriction is essential. Patients with a relatively normal intravascular volume should initially be limited to 400 mL/m^2/24 hr (insensible losses) plus an amount of fluid equal to the urine output for that day. Extrarenal (blood, GI tract) fluid losses should be replaced, milliliter for milliliter, with appropriate fluids. Markedly hypervolemic patients can require further fluid restriction, omitting the replacement of insensible fluid losses, urine output, and extrarenal losses to diminish the expanded intravascular volume. Fluid intake, urine and stool output, body weight, and serum chemistries should be monitored daily.

In AKI, rapid development of **hyperkalemia** (serum potassium level >6 mEq/L) can lead to cardiac arrhythmia, cardiac arrest, and death. The earliest electrocardiographic change seen in patients with developing hyperkalemia is the appearance of peaked T waves. This may be followed by widening of the QRS intervals, ST segment depression, ventricular arrhythmias, and cardiac arrest (see Chapter 472.2). Procedures to deplete body potassium stores should be initiated when the serum potassium value rises to >6.0 mEq/L. Exogenous sources of potassium (dietary, IV fluids, total parenteral nutrition) should be eliminated. Sodium polystyrene sulfonate (SPS) resin (Kayexalate), 1 g/kg, should be given orally or by retention enema. This resin exchanges sodium for potassium and can take several hours to take effect. A single dose of 1 g/kg can be expected to lower the serum potassium level by about 1 mEq/L. Resin therapy may be repeated every 2 hours, the frequency being limited primarily by the risk of sodium overload.

More severe elevations in serum potassium (>7 mEq/L), especially if accompanied by electrocardiographic changes, require emergency measures in addition to Kayexalate. The following agents should be administered:

- Calcium gluconate 10% solution, 100 mg/kg/dose (maximum 3,000 mg/dose)
- Sodium bicarbonate, 1-2 mEq/kg IV, over 5-10 minutes
- Regular insulin, 0.1 units/kg, with glucose 50% solution, 1 mL/kg, over 1 hour

Calcium gluconate counteracts the potassium-induced increase in myocardial irritability but does not lower the serum potassium level. Administration of sodium bicarbonate, insulin, or glucose lowers the serum potassium level by shifting potassium from the extracellular to the intracellular compartment. A similar effect has been reported with the acute administration of β-adrenergic agonists in adults, but there are no controlled data in pediatric patients. Because the duration of action of these emergency measures is just a few hours, persistent hyperkalemia should be managed by dialysis.

Mild **metabolic acidosis** is common in AKI because of the retention of hydrogen ions, phosphate, and sulfate, but it rarely requires treatment. If acidosis is severe (arterial pH <7.15; serum bicarbonate <8 mEq/L) or contributes to significant hyperkalemia, treatment is indicated. The acidosis should be corrected partially by the IV route, generally by giving enough bicarbonate to raise the arterial pH to 7.20 (which approximates a serum bicarbonate level of 12 mEq/L). The remainder of the correction may be accomplished by oral administration of sodium bicarbonate after normalization of the serum calcium and phosphorus levels. Correction of metabolic acidosis with IV bicarbonate can precipitate tetany in patients with renal failure because rapid correction of acidosis reduces the ionized calcium concentration.

Hypocalcemia is primarily treated by lowering the serum phosphorus level. Calcium should not be given IV, except in cases of tetany, to avoid deposition of calcium salts into tissues. Patients should

Table 572.5 Common Complications of Acute Kidney Injury

METABOLIC	CARDIOPULMONARY	GASTROINTESTINAL	NEUROLOGIC	HEMATOLOGIC	INFECTIOUS	OTHER
Hyperkalemia Metabolic acidosis Hyponatremia Hypocalcemia Hyperphosphatemia Hypermagnesemia Hyperuricemia	Pulmonary edema Arrhythmias Pericarditis Pericardial effusion Hypertension Myocardial infarction Pulmonary embolism	Nausea Vomiting Malnutrition Hemorrhage	Neuromuscular irritability Asterixis Seizures Mental status changes	Anemia Bleeding	Pneumonia Septicemia Urinary tract infection	Hiccups Elevated parathyroid hormone level Low total triiodothyronine and thyroxine levels Normal thyroxine level

From Weisbord SD, Palevsky PM. Acute kidney injury. In: Yu AS, Chertow GM, Luyckx VA, et al, eds. *Brenner & Rector's The Kidney,* 11th ed. Philadelphia: Elsevier; 2020: Table 29.6.

be instructed to follow a low-phosphorus diet, and phosphate binders should be orally administered to bind any ingested phosphate and increase the GI phosphate excretion. Common agents include sevelamer (Renagel), calcium carbonate (Tums tablets or Titralac suspension), and calcium acetate (PhosLo). Aluminum-based binders, commonly employed in the past, should be avoided because of the risk of aluminum toxicity.

Hyponatremia is most commonly a dilutional disturbance that must be corrected by fluid restriction rather than sodium chloride administration. Administration of hypertonic (3%) saline should be limited to patients with symptomatic hyponatremia (seizures, lethargy) or those with a serum sodium level <120 mEq/L. Acute correction of the serum sodium to 125 mEq/L (mmol/L) should be accomplished using the following formula:

$$\text{mEq sodium required} = 0.6 \times \text{weight in kg} \times (125 - \text{serum sodium in mEq/L}).$$

AKI patients are predisposed to **GI bleeding** because of uremic platelet dysfunction, increased stress, and heparin exposure if treated with hemodialysis (HD) or continuous renal replacement therapy (CRRT). Oral or IV H_2 blockers such as ranitidine are commonly administered to prevent this complication.

Hypertension can result from hyperreninemia associated with the primary disease process and/or expansion of the extracellular fluid volume and is most common in AKI patients with acute glomerulonephritis or HUS. Salt and water restriction is critical, and diuretic administration may be useful (see Chapter 494). Isradipine (0.05-0.15 mg/kg/dose, maximum dose 5 mg 4 times per day) may be administered for a relatively rapid reduction in blood pressure (BP). Longer-acting oral agents such as calcium channel blockers (amlodipine, 0.1-0.6 mg/kg/24 hr daily or divided twice daily) or β blockers (labetalol, 4-40 mg/kg/24 hr divided 2 or 3 times daily) may be helpful in maintaining control of the BP. Children with severe symptomatic hypertension (hypertensive urgency or emergency) should be treated with continuous infusions of nicardipine (0.5-5.0 μg/kg/min), sodium nitroprusside (0.5-10.0 μg/kg/min), labetalol (0.25-3.0 mg/kg/hr), or esmolol (150-300 μg/kg/min) and converted to intermittently dosed antihypertensives when more stable.

Neurologic symptoms in AKI can include headache, seizures, lethargy, and confusion (encephalopathy). Potential etiologic factors include hypertensive encephalopathy, hyponatremia, hypocalcemia, cerebral hemorrhage, cerebral vasculitis, and the uremic state. Benzodiazepines are the most effective agents in acutely controlling seizures, and subsequent therapy should be directed toward the precipitating cause.

The **anemia** of AKI is generally mild (hemoglobin 9-10 g/dL) and primarily results from volume expansion (hemodilution). Children with HUS, SLE, active bleeding, or prolonged AKI can require transfusion of packed red blood cells if their hemoglobin level falls below 7 g/dL. In hypervolemic patients, blood transfusion carries the risk of further volume expansion, which can precipitate hypertension, heart failure, and pulmonary edema. Slow (4- to 6-hour) transfusion with packed red blood cells (10 mL/kg) diminishes the risk of hypervolemia. The use of fresh, washed red blood cells minimizes the acute risk of hyperkalemia, and the chronic risk of sensitization if the patient becomes a future candidate for renal replacement therapy. In the presence of severe hypervolemia or hyperkalemia, blood transfusions are most safely administered during dialysis or ultrafiltration.

Nutrition is of critical importance in children who develop AKI. In most cases, sodium, potassium, and phosphorus should be restricted. Protein intake should be moderately restricted while maximizing the caloric intake to minimize the accumulation of nitrogenous wastes. In critically ill patients with AKI, parenteral hyperalimentation with essential amino acids should be considered.

Dialysis

Indications for dialysis in AKI include the following:

- Anuria/oliguria with fluid overload
- Volume overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy
- Persistent hyperkalemia
- Severe metabolic acidosis unresponsive to medical management
- Uremia (encephalopathy, pericarditis, neuropathy)
- Calcium:phosphorus imbalance, with hypocalcemic tetany that cannot be controlled by other measures

An additional important practical indication for dialysis is the inability to provide adequate nutritional intake because of the need for severe fluid restriction. In patients with AKI, dialysis support may be necessary for days or for up to 12 weeks. Many patients with AKI require dialysis support for 1-3 weeks. Table 572.6 lists the advantages and disadvantages of the three types of dialysis.

Intermittent HD is useful in patients with a relatively stable hemodynamic status. This highly efficient process accomplishes both fluid and electrolyte removal in sessions of 3-4 hours using a pump-driven extracorporeal circuit and large central venous catheter. Intermittent HD may be performed 3-7 times per week based on the patient's fluid and electrolyte balance.

Peritoneal dialysis (PD) is most employed in neonates and infants with AKI, although this modality may be used in children and adolescents of all ages. Hyperosmolar dialysate is infused into the peritoneal cavity via a surgically or percutaneously placed PD catheter. The fluid is allowed to dwell for 45-60 minutes and is then drained from the patient by gravity (manually or with the use of machine-driven cycling), accomplishing fluid and electrolyte removal. Cycles are repeated for 8-24 hours per day based on the patient's fluid and electrolyte balance. Anticoagulation is not necessary. PD is contraindicated in patients with significant abdominal pathology.

Continuous renal replacement therapy (CRRT) is useful in patients with an unstable hemodynamic status, increased intracranial pressure, cerebral edema, concomitant sepsis, or multiorgan failure (including

Table 572.6 Comparison of Peritoneal Dialysis, Intermittent Hemodialysis, and Continual Renal Replacement Therapy

	PD	IHD	CRRT
BENEFITS			
Fluid removal	+	++	++
Urea and creatinine clearance	+	++	+
Potassium clearance	++	++	+
Toxin clearance	+	++	+
COMPLICATIONS			
Abdominal pain	+	–	–
Bleeding	–	+	+
Dysequilibrium	–	+	–
Electrolyte imbalance	+	+	+
Need for heparinization	–	+	+/–
Hyperglycemia	+	–	–
Hypotension	+	++	+
Hypothermia	–	–	+
Central line infection	–	+	+
Inguinal or abdominal hernia	+	–	–
Peritonitis	+	–	–
Protein loss	+	–	–
Respiratory compromise	+	–	–
Vessel thrombosis	–	+	+

PD, Peritoneal dialysis; IHD, intermittent hemodialysis; CRRT, continual renal replacement therapy.
Adapted from Rogers MC. *Textbook of Pediatric Intensive Care*. Baltimore: Williams & Wilkins; 1992.

hepatic failure) in the intensive care setting. CRRT is an extracorporeal therapy in which fluid, electrolytes, and small- and medium-size solutes are continuously removed from the blood (24 hours/day) using a specialized pump-driven machine. Usually, a double-lumen catheter is placed into the internal jugular or femoral vein. The patient is then connected to the pump-driven CRRT circuit, which continuously passes the patient's blood across a highly permeable filter.

CRRT may be performed in three basic fashions. In continuous venovenous **hemofiltration**, a large volume of fluid is driven by systemic or pump-assisted pressure across the filter, bringing with it by *convection* other molecules, such as urea, creatinine, phosphorus, and uric acid. The blood volume is reconstituted by an IV infusion of a replacement fluid having a desirable electrolyte composition similar to that of blood. Continuous venovenous **HD** uses the principle of diffusion by circulating dialysate in a countercurrent direction on the ultrafiltrate side of the membrane. No replacement fluid is used. Continuous **hemodiafiltration** employs both replacement fluid and dialysate, offering the most effective solute removal of all forms of CRRT.

Table 572.6 compares the relative risks and benefits of the various renal replacement therapies. CRRT has similar outcomes for recovery of renal function when compared with intermittent HD.

PROGNOSIS

The mortality rate in children with AKI is variable and depends entirely on the nature of the underlying disease process rather than on the renal failure itself. Children with AKI caused by a kidney-limited condition such as postinfectious glomerulonephritis have a very low mortality rate (<1%); those with AKI related to multiorgan failure have a very high mortality rate (>50%).

The prognosis for recovery of kidney function depends on the disorder that precipitated AKI. Recovery is likely after AKI resulting from prerenal causes, ATN, acute interstitial nephritis, or tumor lysis syndrome. Complete recovery of renal function is unusual when AKI results from most types of rapidly progressive glomerulonephritis, bilateral renal vein thrombosis, or bilateral cortical necrosis. Medical management may be necessary for a prolonged period to treat the sequelae of AKI, including chronic renal insufficiency, hypertension, renal tubular acidosis, and urinary concentrating defect.

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572.2 Chronic Kidney Disease

Donna J. Claes

Chronic kidney disease (CKD) is determined by the presence of kidney damage and level (or severity) of kidney function (GFR; Tables 572.7 and 572.8). **End-stage kidney disease (ESKD)** is an administrative term in the United States; it is used to define patients who are treated with dialysis or kidney transplantation and is a subset of patients with stage 5 CKD.

Table 572.7 Criteria for Definition of Chronic Kidney Disease (NKF KDOQI Guidelines)

Patient has chronic kidney disease (CKD) if either of the following criteria are present:

1. Kidney damage for ≥3 mo, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by one or more of the following features:
   - Abnormalities in the composition of the blood or urine
   - Abnormalities in imaging tests
   - Abnormalities on kidney biopsy
2. GFR < 60 mL/min/1.73 m^2 for ≥3 mo, with or without the other signs of kidney damage described previously

GFR, Glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Table 572.8 Standardized Terminology for Stages of Chronic Kidney Disease (NKF KDOQI Guidelines)

STAGE	DESCRIPTION	GFR (ML/MIN/1.73 M²)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 or on dialysis

GFR, Glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

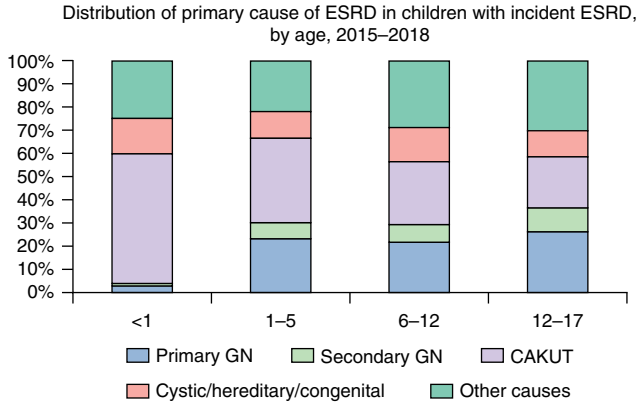

Fig. 572.2 Distribution of primary cause of end-stage renal disease (ESRD), by age, in incident pediatric dialysis patients reported to United States Renal Data System (USRDS) in 2016–2020. CAKUT, Congenital anomalies of the kidney and urinary tract; GN, glomerulonephritis. *(Adapted from the United States Renal Data System. 2022 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2022. Fig. 8.4. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/8-esrd-among-children-and-adolescents)*

Pediatric CKD prevalence is approximately 18 per 1 million children. The prognosis for the infant, child, or adolescent with CKD has improved secondary to improved medical management, dialysis techniques, and kidney transplantation. Childhood-onset ESKD still carries significant morbidity and a 30-fold increased mortality rate as compared with healthy peers.

ETIOLOGY

The etiology of pediatric CKD may be the result of congenital, acquired, inherited, or metabolic renal disease; however, the common etiology is having a reduction in nephron mass (Fig. 572.2). Causes of kidney disease in children are typically subdivided as being non-glomerular vs glomerular in origin (Table 572.9). The underlying cause correlates with the age at the time of diagnosis. **Congenital anomalies of the kidney and urinary tract** (CAKUT; i.e., renal hypoplasia, dysplasia, obstructive uropathy) are predominantly diagnosed in children less than 5 years of age; in many cases, CAKUT is diagnosed with prenatal ultrasonography. Cystic kidney disease (due to single gene pathogenic variants associated with cilia function, or ciliopathies) can be diagnosed prenatally, during childhood, or as a young adult depending on the underlying genetic variant and disease phenotype. After 5 years of age, acquired or inherited forms of glomerulonephritis predominate.

Table 572.9 Etiologies of Pediatric Chronic Kidney Disease

NONGLOMERULAR	GLOMERULAR
Aplastic, hypoplastic, and dysplastic kidneys	Chronic glomerulonephritis (including focal segmental glomerulonephritis [FSGS])
Cystinosis	Congenital nephrotic syndrome (CNS)
Medullary cystic kidney disease/ juvenile nephronophthisis	Hemolytic uremic syndrome (HUS)
Obstructive uropathy (e.g., PUV, cloaca, neurogenic bladder)	Idiopathic crescentic glomerulonephritis
Oxalosis	IgA nephritis
Autosomal dominant and autosomal recessive polycystic kidney disease (ADPKD, ARPDK)	IgA nephropathy (IGAN)
Pyelonephritis/interstitial nephritis/reflux nephropathy	Membranoproliferative glomerulonephritis (MPGN)
Renal infarct	Membranous nephropathy
Syndrome of agenesis of abdominal musculature (Eagle-Barrett syndrome)	Sickle cell nephropathy
Wilms tumor	Systemic immunologic disease (e.g., SLE, granulomatosis with polyangiitis)
	Hereditary nephritis (Alport syndrome)

PUV, Posterior urethral valve; SLE, systemic lupus erythematosus.

PATHOGENESIS

In addition to progressive injury with ongoing structural or metabolic genetic diseases, renal injury can progress despite removal of the original insult.

Hyperfiltration injury may be an important final common pathway of glomerular destruction, independent of the underlying cause of renal injury. As nephrons are lost, the remaining nephrons undergo structural and functional hypertrophy characterized by an increase in glomerular blood flow. The driving force for glomerular filtration is thereby increased in the surviving nephrons. Although this compensatory hyperfiltration temporarily preserves total renal function, it can cause progressive damage to the surviving glomeruli, possibly by a direct effect of the elevated hydrostatic pressure on the integrity of the capillary wall and/or the toxic effect of increased protein traffic across the capillary wall. Over time, the remaining nephrons suffer an increased excretory burden, resulting in a vicious cycle of increasing glomerular blood flow and hyperfiltration injury.

Other pathologic etiologies of CKD include proteinuria, hypertension, hyperphosphatemia, and hyperlipidemia. **Proteinuria**, secondary to either damage to the glomerular capillary wall and/or decreased tubular reabsorption, contributes to renal functional decline. Proteinuria can exert a direct toxic effect on tubular cells and initiate many inflammatory and pro-fibrotic cellular pathways that recruit monocytes and macrophages, enhancing the process of glomerular sclerosis and tubulointerstitial fibrosis. Podocyte injury can also result from proteinuria, although the mechanism is less understood. Uncontrolled **hypertension** can exacerbate disease progression by causing arteriolar nephrosclerosis and by increasing the hyperfiltration injury. **Hyperphosphatemia** can increase progression of disease by leading to calcium phosphate deposition in the renal interstitium and blood vessels. **Hyperlipidemia,** a common condition in CKD patients, can adversely affect glomerular function through oxidant-mediated injury.

CKD is viewed as a continuum of disease, with increasing biochemical and clinical manifestations as renal function deteriorates (Fig. 572.3). Regardless of etiology, the progression of tubulointerstitial fibrosis is the primary determinant of CKD progression.

CLINICAL MANIFESTATIONS

Table 572.10 outlines the pathophysiologic manifestations of CKD. The clinical presentation of CKD is varied and depends on the underlying etiology and CKD stage (Fig. 572.4). CAKUT and some genetic forms of renal disease (i.e., familial nephronophthisis) demonstrate growth failure, vomiting, and polyuria with associated polydipsia. Patients with cystic kidney disease due to a ciliopathy can have a wide range of extrarenal anomalies of the kidneys, liver, pancreas, skeletal system, eyes, central nervous system, and/or cardiac system that can assist with disease diagnosis. Urinary tract infection can also be common in those with urologic abnormalities. Glomerular forms of CKD often present with edema, hypertension, hematuria, and proteinuria; in severe forms of glomerulonephritis, malnutrition can be seen. As renal deterioration advances in severity, patients can develop uremic symptoms (i.e., worsening fatigue, weakness, nausea, vomiting, anorexia, and poor sleep patterns) and edema, hypertension, and other findings of fluid overload, regardless of CKD etiology.

Physical examination in CKD should focus on overall growth and development, with special attention and/or evaluation of BP, as well as the skin (pallor) and the extremities (edema; bony abnormalities of rickets seen in untreated renal osteodystrophy).

LABORATORY FINDINGS

Laboratory findings can include elevations in BUN and serum creatinine in addition to hyperkalemia, hyponatremia (secondary to either renal salt wasting vs volume overload), hypernatremia (loss of free water), acidosis, hypocalcemia, hyperphosphatemia, and an elevation in uric acid. Patients with heavy proteinuria can have hypoalbuminemia. A complete blood cell count may show a normochromic, normocytic anemia. Dyslipidemia is commonly seen. In children with glomerulonephritis, the urinalysis (UA) shows hematuria and proteinuria, whereas, in children with congenital lesions such as renal dysplasia, the UA often has a low specific gravity with minimal other abnormalities.

Renal function can be measured or estimated by GFR. Inulin clearance is the gold standard to measure GFR, but it is no longer readily available. Other methods to measure GFR in clinical practice include using iohexol or various radioisotopes (^{99m}Tc-DTPA, ^{51}Cr-EDTA, or ^{125}Iothalamate). However, estimating GFR by endogenous markers (such as creatinine and/or cystatin C) is the most utilized method to understand severity of renal disease. A "bedside" creatinine-based estimating equation [estimated GFR (mL/min/1.73 m^2) = 0.413 × height (cm)/serum creatinine (mg/dL)] has been validated in a pediatric CKD population of children age 1-16 years whose GFR was between 15 and 90 mL/min/1.73 m^2; however, this formula has less accuracy in the very young (<5 years of age) and young adults (18-25 years of age). Newer estimation formulas ("Chronic Kidney Disease in Children [CKID] study under 25," or U25) have been developed that allow for age- and gender-based corrections of creatinine and cystatin C with improved accuracy of GFR estimation. Although these newer formulas are more complex in regard to the mathematical corrections of age and gender for both creatinine and cystatin C, they are accessible by an online calculator, which allows for ease in their clinical use.

TREATMENT/MANAGEMENT

CKD treatment is supportive, with an aim to screen for and treat various metabolic complications of CKD in hopes of improving quality of life and potentially slowing the progression of renal dysfunction. Children with CKD should be treated at a pediatric center capable of supplying multidisciplinary services, including medical, nursing, social service, nutritional, and psychologic support.

CKD management requires close monitoring of blood studies, urine studies (including quantitative measurement for proteinuria using either a spot urine protein/urine creatinine ratio or 24-hour urine collection), and overall clinical symptomatology. Ambulatory blood pressure monitoring (ABPM) over 24 hours, the gold standard of BP evaluation, is recommended in patients with renal disease to diagnose and treat hypertension, especially masked hypertension. **Masked hypertension** (defined as a normal office BP but abnormal ABPM) is seen in up to 35% of pediatric predialysis CKD patients and carries a fourfold increased risk of having left ventricular hypertrophy (LVH).

Nutrition

Nutritional management by a dietician experienced in pediatric renal patients is recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Patients should

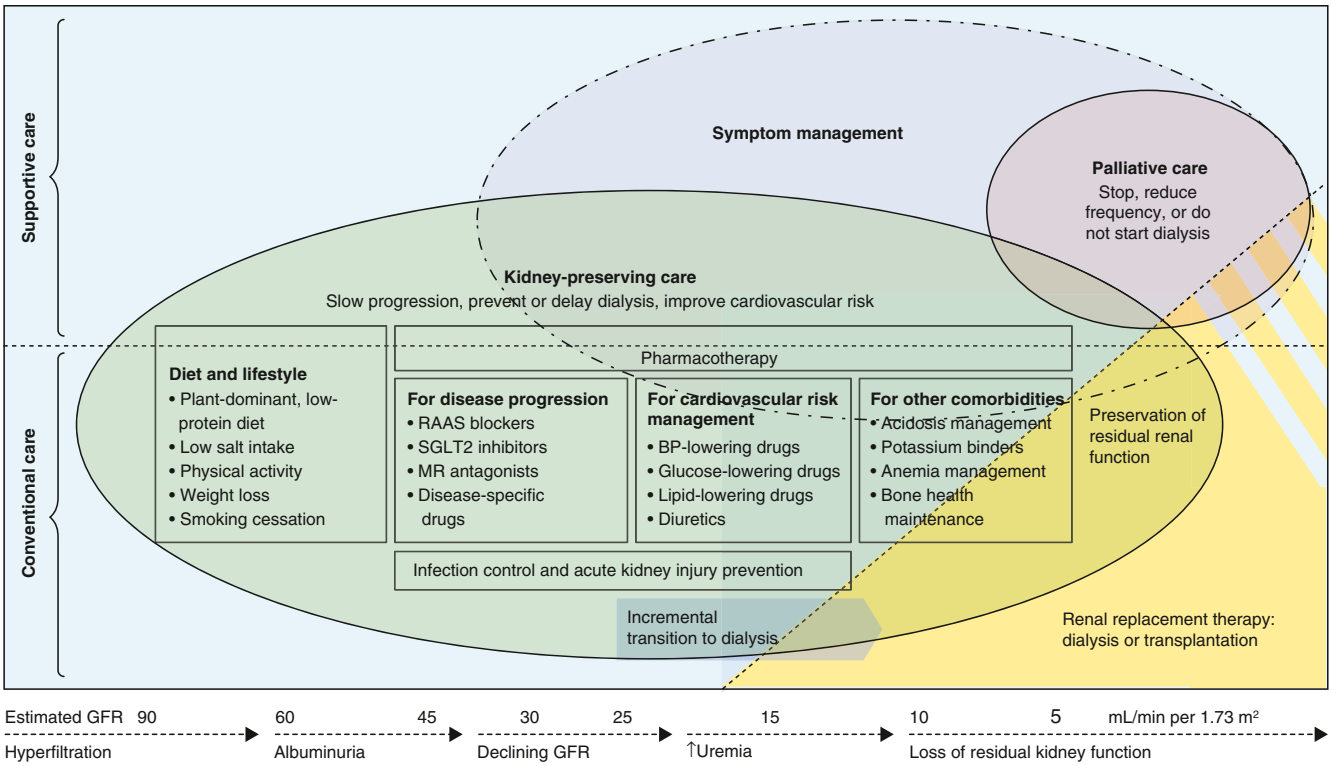

Fig. 572.3 Conservative and preservative management of chronic kidney disease without dialysis or renal transplantation. This chart highlights the role of preservative management and its goals *(green domain)* within the overall conservative management of chronic kidney disease without dialysis *(blue zone)*, juxtaposing renal replacement therapy including dialysis and kidney transplantation *(yellow zone)*. The X-axis (showing chronic kidney disease progression) should be read exclusively from left to right. The bottom half of the chart represents conventional (life-prolonging and kidney-prolonging) strategies, whereas the top half represents supportive care, including palliative and hospice care, in which dialysis is often avoided or withdrawn *(violet domain)*. The *oblique dotted line* between the two main zones (conservative management vs renal replacement therapy) suggests that there is variability in transitioning to dialysis therapy (moving from bottom left to top right), including timing (early vs late vs never), level of care (life-prolonging vs supportive care), and type of dialysis (conventional vs incremental). The symptom management *(purple)* domain provides wide ranges of interventions to encompass the goals of care under both kidney-preserving care and palliative and hospice care. Preservative management can preserve residual kidney function for longer, especially after incremental transition to dialysis. BP, Blood pressure; GFR, glomerular filtration rate; MR, mineralocorticoid receptor; RAAS, renin-angiotensin-aldosterone system. *(From Kalantar-Zadeh K, Jafar TH, Nitsch D, et al. Chronic kidney disease. Lancet. 2021;398:786–798. Fig. 1, p. 787.)*

receive 100% of estimated energy requirement for age, individually adjusted for physical activity level, body mass index, and response in the rate of weight gain or loss. When oral supplemental nutrition with increased calories or fluid volume is insufficient, tube feeding (by nasogastric tubes or gastrostomy tubes) should be considered. Calories should be balanced between carbohydrate, unsaturated fat in physiologic ranges (per dietary reference intake [DRI]), and protein. Dietary protein restriction is not suggested for children with CKD because of the concern about adverse effects on growth and development; in fact, recommended protein intake is often 100% (or more for those receiving dialysis) of the DRI for ideal weight for children. Children with CKD stages 2-5 should receive 100% of DRI of vitamins and trace elements; water-soluble vitamin supplements are often required for patients receiving dialysis.

CKD Mineral and Bone Disorder (CKD-MBD)

CKD is characterized by systemic disorders of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism that can lead to bone disorders (**renal osteodystrophy**) but also *vascular and soft tissue calcification* (Fig. 572.5). Efforts have focused on the role of the hormone fibroblast growth factor 23 (FGF-23) and its cofactor, Klotho, in CKD-mineral and bone disorder (MBD). Elevated FGF-23 results in increased urinary phosphate excretion and suppression of 1-α-hydroxylase activity, leading to reduced 1,25-dihydroxycholecalciferol ($1,25OH_2D$) values and increased PTH secretion. Elevated FGF-23 is the first sign of altered osteocyte function in pediatric and adult CKD, is seen as early as CKD stage 2 (GFR 60-90 mL/min/1.73 m^2), and occurs despite normal calcium, phosphorus, PTH, and $1,25OH_2D$ levels. With continued loss of renal function, further FGF-23 elevation results in the development of secondary hyperparathyroidism (low $1,25OH_2D$ with hypocalcemia, hyperphosphatemia, and elevated PTH values).

Renal osteodystrophy is characterized by abnormalities in *bone turnover* (high vs low), *mineralization,* and *bone volume.* High-turnover bone disease, or **osteitis fibrosa cystica**, is the most common condition seen in advanced pediatric CKD, with characteristic laboratory (hypocalcemia, hyperphosphatemia, and elevated alkaline phosphatase and PTH values) and radiographic (subperiosteal bone resorption, metaphyseal widening) findings. Clinical manifestations may include bone pain, fractures with minor trauma, and various bony abnormalities (rachitic changes, varus and valgus deformities of the long bones, and slipped capital femoral epiphyses [SCFE]). In contrast, low-turnover bone disease **(adynamic renal osteodystrophy)** is associated with PTH over-suppression, hypercalcemia, and low alkaline phosphatase activity; it is more commonly seen in pediatric dialysis patients receiving treatment for secondary hyperparathyroidism. Defective bone mineralization occurs in states of either high bone turnover (mixed lesion) or low to normal bone turnover (osteomalacia). In terms of bone volume, most pediatric CKD patients have normal to high bone volume on bone histomorphometry unless they were exposed to prolonged corticosteroid use.

Vascular calcification in CKD-MBD typically occurs within the vascular media, which is in contrast to the atherosclerotic plaques that form within the vascular intima in patients with traditional cardiovascular risk factors (hypertension, diabetes/obesity, cigarette smoking,

Table 572.10 Pathophysiology of Chronic Kidney Disease

MANIFESTATION	MECHANISMS
Accumulation of nitrogenous waste products	Decrease in glomerular filtration rate
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion
Sodium wasting	Solute diuresis Tubular damage
Urinary concentrating defect	Solute diuresis Tubular damage
Hyperkalemia	Decrease in glomerular filtration rate Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25-dihydroxycholecalciferol ($1,25OH_2D$) Hyperphosphatemia Hypocalcemia Secondary hyperparathyroidism
Growth retardation	Inadequate caloric intake Renal osteodystrophy Metabolic acidosis Anemia Growth hormone resistance
Anemia	Decreased erythropoietin production Iron, folate, and/or vitamin B_{12} deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Decreased academic achievement, attention regulation, or executive functioning	Hypertension Low birth weight
Gastrointestinal symptoms (feeding intolerance, abdominal pain)	Gastroesophageal reflux Decreased gastrointestinal motility
Hypertension	Volume overload Excessive renin production
Hyperlipidemia	Decreased plasma lipoprotein lipase activity Abnormal HDL-C
Cardiomyopathy	Hypertension Anemia Fluid overload
Glucose intolerance	Tissue insulin resistance

HDL-C, High-density lipoprotein cholesterol.

and dyslipidemia). Vascular calcification in CKD has been associated with hypercalcemia, hyperphosphatemia, and an elevated calcium-phosphorus product ($Ca \times PO_4$); yet, studies of adult and pediatric patients with mild to moderate CKD have noted findings of vascular calcification despite normal serum calcium and phosphorus values. The cause of vascular calcification in CKD is not completely understood and is being actively studied. The proposed pathophysiologic etiology involves the transition of vascular smooth muscle cells to osteoblast-like cells in response to trigger(s) that are currently unknown.

Treatment for CKD-MBD is guided by clinical assessment of calcium, phosphorus, 25OH vitamin D, and PTH. The goals of treatment are to normalize mineral metabolism with the goal of improving growth, reducing bone deformities and fragility, and reducing vascular and other soft tissue calcification. This is typically accomplished with reduced phosphorus intake, normalization of 25OH vitamin D, and use of active vitamin D sterols.

CKD patients of all ages should typically follow a low-phosphorus diet with the goal to maintain age-appropriate serum phosphorus values. Infants should be provided with a low-phosphorus formula (Similac PM 60/40). **Phosphate binders** (given with meals) are used to enhance GI phosphate excretion, and at present are recommended to be started at the onset of hyperphosphatemia. Phosphate binders should be adjusted to maintain normal serum calcium and phosphorus levels and to ensure that the recommended total daily intake of calcium is not exceeded. Phosphate binders can be either calcium based (calcium carbonate, calcium acetate) or non–calcium based (sevelamer). Because aluminum may be absorbed from the GI tract and can lead to aluminum toxicity (manifested by anemia, various bony abnormalities, and neurologic abnormalities including seizures), aluminum-based binders should be avoided.

Correcting 25OH vitamin D insufficiency can delay the onset of secondary hyperparathyroidism in predialysis CKD patients and improves bone mineralization. 25OH vitamin D provides a substrate for the formation of $1,25OH_2D$ and has been shown to directly suppress PTH production at the level of the parathyroid gland. U.S.-based pediatric CKD treatment guidelines define 25OH vitamin D sufficiency as a serum value of ≥30 ng/mL; **ergocalciferol** or **cholecalciferol** are typically recommended to treat insufficient 25OH vitamin D.

Active vitamin D sterols have been traditionally indicated when (1) $1,25OH_2D$ levels fall below the established goal range for the child's particular stage of CKD, (2) PTH levels increase above the established goal range for CKD stage (after correcting for insufficient 25OH vitamin D), or (3) patients have elevated PTH levels and hypocalcemia. Vitamin D sterols increase calcium and phosphorus absorption from the GI tract and are effective in reducing PTH values. Calcitriol is the most well-known and studied active vitamin D sterol; other agents such as paricalcitol and doxercalciferol have less intestinal calcium and phosphorus reabsorption and are used in CKD patients predisposed to hypercalcemia. The ideal PTH target to initiate and monitor active vitamin D sterol therapy is debated, particularly in the predialysis CKD population.

Fluid and Electrolyte Management

Infants and children with renal dysplasia may be polyuric with significant urinary sodium and free water losses. These children benefit from high-volume, low-caloric-density feedings with sodium supplementation. Children with high BP or edema benefit from sodium restriction and diuretic therapy. Fluid restriction is necessary in severe cases of nephrotic syndrome or when renal function worsens to the point of requiring dialysis.

Hyperkalemia can develop with severe deterioration in renal function, as well as in patients with moderate renal insufficiency who have excessive dietary potassium intake, severe acidosis, or hyporeninemic hypoaldosteronism (related to destruction of the renin-secreting juxtaglomerular apparatus). Hyperkalemia may be treated by restriction of dietary potassium intake, administration of oral alkalinizing agents, and/or use of **cation exchange resins**. The most commonly utilized cation exchange resin, SPS (Kayexalate) has many severe adverse drug events, including but not limited to GI abnormalities (including intestinal necrosis), hypernatremia, hypocalcemia, and hypomagnesemia, that can limit its use or result in significant morbidity. Newer cation exchange resins (such as sodium zirconium cyclosilicate and patiromer) are more selective for potassium ion exchange and have a more favorable side effect profile compared with SPS. Patiromer is approved for ages ≥12 years in the United States, and sodium cyclosilicate is currently approved for adults; pediatric studies are ongoing.

Metabolic acidosis develops as a result of decreased net acid excretion by the failing kidneys. Either Bicitra (1 mEq sodium citrate/mL) or sodium bicarbonate tablets (650 mg = 7.7 mEq of sodium and 7.7 mEq of bicarbonate) may be used to maintain the serum bicarbonate level ≥22 mEq/L.

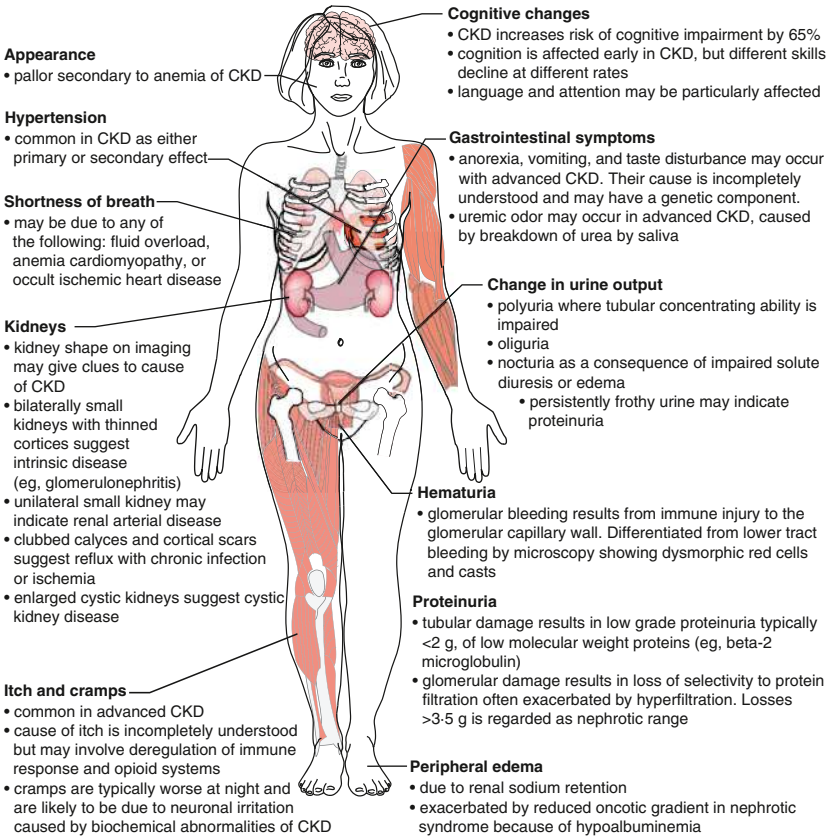

Fig. 572.4 Symptoms and signs of CKD. *(From Webster AC, Navler EV, Morton RL, et al. Chronic kidney disease. Lancet. 2017;389:1238–1252. Fig. 2.)*

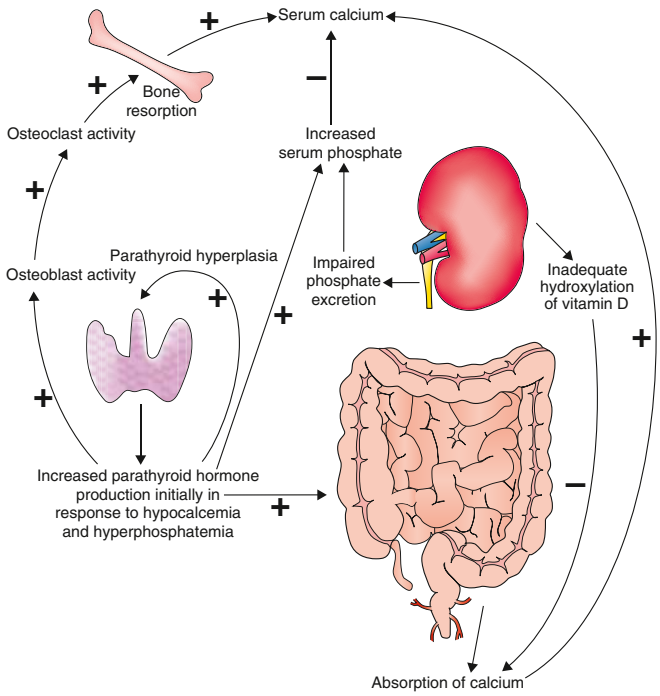

Fig. 572.5 Pathophysiology of CKD mineral bone disease. *(From Webster AC, Navler EV, Morton RL, et al. Chronic kidney disease. Lancet. 2017;389:1238–1252. Fig. 4.)*

Linear Growth

Short stature is a significant long-term sequela of childhood CKD. CKD results in an apparent growth hormone–resistant state, with elevated growth hormone levels but decreased insulin-like growth factor-1 levels and abnormalities of insulin-like growth factor–binding proteins.

Children with CKD who remain less than −2 SD for height and/or have a growth velocity of <25% over a minimum of 6 months despite optimal medical support (adequate caloric intake and effective treatment of renal osteodystrophy, anemia, and metabolic acidosis) may benefit from treatment with recombinant human growth hormone (rHuGH). rHuGH is given by daily, subcutaneous injections and continues until the patient reaches the 50th percentile for mid-parental height, achieves a final adult height, or undergoes kidney transplantation (with the caveat that rHuGH can be restarted 1 year after kidney transplantation if there are concerns for ongoing short stature despite kidney transplantation). Long-term rHuGH treatment significantly improves final adult height and induces persistent catch-up growth; some patients are able to achieve normal adult height.

Anemia

Anemia in patients with CKD is primarily the result of inadequate erythropoietin production by the peritubular interstitial cells of the kidneys and typically manifests when renal function falls below 40 mL/min/1.73 m^2. Other contributory factors for anemia in CKD include iron, folic acid, and/or vitamin B_{12} deficiency, and decreased erythrocyte survival secondary to uremia.

Anemia in pediatric CKD patients is defined when the hemoglobin falls to <5% for age and gender; alternatively, anemia can also be defined when the hemoglobin falls to <11g/dL (ages 0.5-5 years of age), <11.5 g/dL (5-12 years of age), <12 g/dL (females >12 years of age, males 12-15 years of age), and <13 g/dL (males >15 years of age). Once anemia is diagnosed, the recommendation is to investigate for deficiencies in iron and/or other vitamins (i.e., vitamin B_{12}, folate). Iron supplementation (oral or IV) is recommended for patients who demonstrate a transferrin saturation (TSAT) ≤20% and ferritin ≤100 ng/mL.

Erythropoiesis-stimulating agents (ESAs) have decreased the need for transfusions in CKD patients, especially those receiving HD. Erythropoietin and darbepoetin alfa are commonly prescribed ESAs. All patients receiving ESA therapy should be provided with either oral or IV iron supplementation. Patients who appear to be resistant to ESA should be evaluated for iron deficiency, occult blood loss, a chronic infection or inflammatory state, vitamin B_{12} or folate deficiency, or bone marrow fibrosis related to secondary hyperparathyroidism.

Emerging therapies for anemia of CKD are being directed toward the hypoxia-inducible signaling factor (HIF) pathway. HIF stabilizers prevent degradation of the HIF alpha subunit and allow for erythropoietin production. These agents are currently being studied for clinical use in adult CKD patients.

Hypertension and Proteinuria

Hypertension in pediatric CKD can be secondary to volume overload and/or excessive renin production due to glomerular disease. Both hypertension and proteinuria have been independently associated with more rapid CKD progression in various pediatric CKD observational studies. The ESCAPE trial demonstrated that more aggressive BP control delays CKD progression. In this study, participants with 24-hour mean arterial pressure (MAP) <50th percentile for age and sex by ABPM had a 35% lower risk of reaching the composite outcome (doubling of serum creatinine, estimated GFR (eGFR) of <10 mL/min/1.73 m^2, or need for dialysis or kidney transplant) compared with those randomized to a conventional BP target (MAP of 50–95% by ABPM); this effect was more notable in those with significant proteinuria.

Therapy for hypertension involves both dietary interventions and often pharmacologic agents. **Dietary sodium restriction** (<2 g of sodium/24 hr) and lifestyle modifications that promote achieving a healthy weight are both important aspects of achieving good BP control. Treatment guidelines recommend initiating pharmacologic antihypertensive therapy when systolic or diastolic BPs are >90% for age, gender, and height. Once therapy is started, it is recommended to titrate medications to achieve a systolic and diastolic BP <50% for age, gender, and height, especially in those patients with proteinuria. **ACE inhibitors** (such as enalapril, lisinopril) and **angiotensin II receptor blockers** (ARBs; such as losartan) are the antihypertensive medications of choice in all children with pediatric CKD, irrespective of the level of proteinuric renal disease, because of their potential ability to slow CKD and their superiority in controlling BP as noted in various observational and research studies. It is important to closely monitor renal function and electrolyte balance while using ACE inhibitors or ARBs, particularly in those with advanced CKD. **Thiazide** (hydrochlorothiazide, chlorothiazide, metolazone, and chlorthalidone) or **loop diuretics** (furosemide) can be helpful to control hypertension related to salt and fluid retention. Historical guidelines recommend the cessation of thiazide diuretics when a patient's eGFR falls below 30 mL/min/1.73 m^2 due to concerns of decreased efficacy; however, many adult studies support continued thiazide use either alone or in conjunction with loop diuretics for BP control in advanced (non-ESKD) CKD. Calcium channel blockers (amlodipine), β blockers (propranolol, atenolol), and centrally acting agents (clonidine) may be useful as adjunctive agents in children with CKD whose BP cannot be controlled using dietary sodium restriction, ACE inhibitors, and diuretics.

Immunizations

Children with CKD should receive all standard immunizations according to the schedule used for healthy children, with an exception to withhold live virus vaccines (such as measles, mumps, rubella, varicella) from those receiving immunosuppressive medications (i.e., kidney transplant recipients, and in some patients with glomerulonephritis). It is critical to make every attempt to administer live virus vaccines before kidney transplantation. All children with CKD should receive a yearly influenza vaccine; children with CKD are also eligible for pneumococcal vaccination with PPSV-23. Data from a number of studies suggest that children with CKD might respond suboptimally to immunizations.

Adjustment in Drug Dose

Drugs excreted by the kidneys may need to be dose adjusted in CKD patients to maximize effectiveness and minimize the risk of toxicity. Strategies in dosage adjustment include lengthening of the interval between doses, decreasing the absolute dose, or both.

Progression of Disease

The timing of CKD progression from minimal renal injury to onset of ESKD is variable. The median loss of GFR in children enrolled in the CKID study is 1.5 (non-glomerular CKD etiology) vs 4.3 (glomerular CKD etiology) mL/min/1.73 m^2/year. Nonmodifiable risk factors associated with more rapid CKD progression include older age, glomerular etiology of renal disease, CKD severity, and onset of puberty. In terms of potential modifiable risk factors, in addition to elevated BP, persistent nephrotic range proteinuria, anemia, dyslipidemia, and no ACE inhibitor/ARB use were important predictors of CKD progression.

In addition to addressing and treating the risk factors as noted previously, prompt treatment of infectious complications (especially urinary tract infection [UTI]) and episodes of dehydration can minimize additional loss of renal parenchyma. Other potentially beneficial recommendations include tobacco avoidance; prevention of obesity; and avoidance of potential nephrotoxic medications, which includes over-the-counter medications (such as nonsteroidal antiinflammatory medicines), pharmacologic agents, various illegal street drugs, and herbal and/or homeopathic medications or supplements.

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572.3 End-Stage Kidney Disease

Donna J. Claes

Kidney failure, also termed end-stage kidney disease (ESKD), represents the state in which a patient's kidney dysfunction has progressed to the point at which homeostasis and survival can no longer be sustained despite maximal medical management. At this point, kidney replacement therapy (KRT; which is either dialysis or kidney transplantation) becomes necessary. The ultimate goal for children with ESKD is successful kidney transplantation (see Chapter 573) because it provides the most normal lifestyle and improved mortality and morbidity.

In the United States, 75% of children with ESKD require dialysis before transplantation. It is recommended discussions and plans for eventual KRT be initiated when a child reaches stage 4 CKD (GFR <30 mL/min/1.73 m^2). Indications for initiating maintenance dialysis include diuretic-resistant fluid overload, severe fluid restrictions that inhibit the ability to provide appropriate nutrition sufficient for linear growth, uncontrolled electrolyte abnormalities (hyperkalemia, hyperphosphatemia, metabolic acidosis), and subjective findings of uremia (fatigue, weakness, nausea, vomiting, anorexia, and poor sleep patterns), especially if these symptoms are negatively affecting academic performance. Although dialysis initiation should be considered as the GFR approaches 10-15 mL/min/1.73m^2, multiple adult and pediatric studies have indicated increased risk of mortality in those who start dialysis with a higher GFR compared to a lower GFR. Thus it is recommended to maximize medical management of CKD for as long as possible until concerns of severe fluid and electrolyte abnormalities, malnutrition, and uremic symptoms make medical management unsafe and/or impossible. Dialysis modality selection must be individualized to fit the needs of each child.

In the United States, peritoneal dialysis (PD) is still the most utilized dialysis modality (55.7%) compared to hemodialysis (44.3%); however, there is a temporal trend toward greater use of hemodialysis (HD) as the initial maintenance dialysis therapy. Age is a defining factor in dialysis modality selection: 85% of infants and children from birth to 5 years of age initiate maintenance dialysis treatment using PD, whereas 50% of children ≥13 years of age initiate maintenance dialysis treatment with HD.

Peritoneal dialysis utilizes the patient's peritoneal membrane to transport fluid and solutes. Excess body water is removed by an osmotic gradient created by the relatively high dextrose concentration in the dialysis fluid; wastes are removed by diffusion from the peritoneal capillaries into the dialysis fluid. Access to the peritoneal cavity is achieved by a surgically inserted tunneled catheter. PD may be provided either as continuous ambulatory peritoneal dialysis (CAPD) or as an automated therapy using a cycler (APD), which allows exchanges of peritoneal fluid to be performed automatically during sleep by a cycler machine. APD is the PD modality of choice in countries without cost restraints. Cycler-driven PD therapy allows the child and family an

uninterrupted day of activities (including decreased school interruption), a reduction in the number of dialysis catheter connections and disconnections (which decreases the risk of peritonitis), often less strict fluid and dietary restrictions, and a reduction in the time required by patients and parents to perform dialysis, reducing the risk of caregiver fatigue and burnout. Because PD is not as efficient as HD, it must often be performed 6-7 days per week. Contraindications to PD use include anatomic abnormalities (e.g., significant surgical adhesions, omphalocele, gastroschisis, or bladder exstrophy), peritoneal injury (including injury secondary to previous severe peritoneal infections), or lack of an appropriate caregiver who can reliably perform PD in the home.

Hemodialysis, unlike PD, is usually performed in a hospital or outpatient clinic setting; home pediatric HD programs or programs that provide intensified HD are available but uncommon. Access to the child's circulation is achieved by a surgically created arteriovenous fistula (AVF), arteriovenous graft (AVG), or tunneled dual lumen catheter. The internal jugular vein is the preferred catheter site because indwelling subclavian catheters can cause subclavian stenosis that limits that ability to utilize future AVF and AVG in the ipsilateral arm. Each HD treatment is typically prescribed to provide appropriate solute clearance and fluid removal. HD has historically been provided 3 times per week; however, more frequent dialysis treatments (up to 4-5 times per week) are seen in the United States. Intensified HD programs (such as short daily HD, intermittent nocturnal HD, and daily nocturnal HD) have demonstrated improved control of BP, fluid overload, phosphorus, anemia, and improved growth. Contraindications to HD include inadequate vascular access.

Pediatric patients on dialysis have a death rate 30 times higher than the general pediatric population, with cardiovascular disease and infections as the leading causes of mortality. Dialysis-associated infections (peritonitis, HD-related bloodstream infections) are also the leading causes of hospitalization in pediatric dialysis patients.

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Chapter 573

Renal Transplantation

David K. Hooper and Charles D. Varnell Jr.

Kidney transplantation is the optimal therapy for children with end-stage kidney disease (ESKD). The life expectancy in children who receive a kidney transplant has steadily increased and is substantially better than for those who remain on dialysis (Fig. 573.1). Children and adolescents with ESKD have special needs that differ from adults, including the need to achieve normal growth and cognitive development. Successful transplantation leads to accelerated linear growth, allows for regular school attendance, and often eliminates the need for dietary restrictions. Improvements in surgical techniques and a reduction in the early complications such as thrombosis have given young children the best long-term outcomes of all age-groups among transplant recipients. Following kidney transplantation, the most commonly encountered complications include acute or chronic allograft rejection, an increased risk for infections with both community-acquired and opportunistic organisms, and cardiovascular disease (hypertension, obesity, dyslipidemia). Providers must also be aware of the risks for malignancy and sequelae of chronic kidney disease (CKD).

INCIDENCE AND ETIOLOGY OF ESKD

The incidence of ESKD in pediatric patients in the United States varies by age-group (Table 573.1), with an adjusted incident rate of 11 per million population in 2020. The etiology of ESKD in children also varies

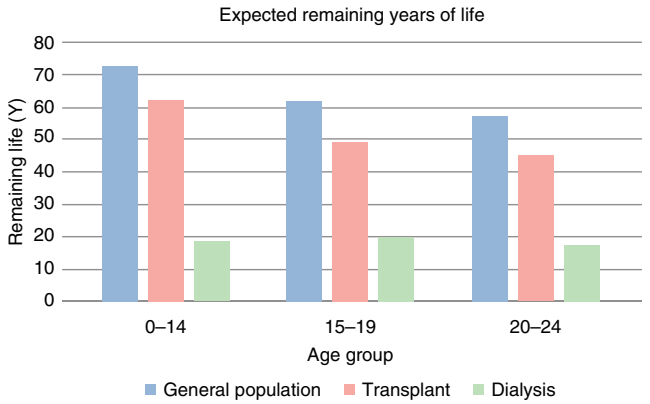

Fig. 573.1 Expected remaining years of life by end-stage renal disease treatment modality. Patients on dialysis or with a kidney transplant are compared to healthy children by age. *(Adapted from United States Renal Data System. 2020 USRDS annual data report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020.)*

Table 573.1 Incident Rates of Reported ESKD in the United States

AGE RANGE (YEAR)	ADJUSTED INCIDENT RATES PER MILLION POPULATION
<1	26
1-5	7
6-12	8
13-17	16

Data from United States Renal Data System. 2022 USRDS annual data report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2022. Fig. 8.2. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/8-esrd-among-children-and-adolescents.

by age (Table 573.2; see Fig. 572.2 in Chapter 572). **Cystic or hereditary diseases** account for more than 24% of children wait-listed for a kidney transplant, whereas **congenital anomalies of the kidney and urinary tract (CAKUT)** account for 18% of such children. In 2020, there were 710 kidney transplants performed in children <18 years of age in the United States, with 184 performed in children ≤5 years old, 129 in children ages 6-10 years, and 397 in children ages 11-17 years. That same year, of the 6,177 children in the United States with ESKD, 4,577 (74.1%) had a functioning kidney transplant.

INDICATIONS FOR RENAL TRANSPLANTATION

Renal transplantation is generally considered for any child when chronic renal replacement therapy is indicated. There are few absolute contraindications for pediatric kidney transplantation, yet relative contraindications arise when the combined risks of the transplant procedure itself and lifelong immunosuppression outweigh the benefits of improved health, longevity, and/or quality of life. Such relative contraindications include preexisting malignancy, primary or secondary immunodeficiency, chronic severe infection, inability to receive appropriate posttransplant care, or severe neurologic dysfunction where improvement in the quality of life and/or longevity is unlikely. In each scenario, the multidisciplinary team must weigh the risks and benefits of transplantation while accounting for the values of patients and caregivers. For instance, patients who have remission of malignancy for a minimum of 1-2 years may be considered on an individual basis for kidney transplantation. Similarly, patients with autoimmune diseases resulting in ESKD (e.g., systemic lupus erythematosus) are candidates for transplantation after a period of immunologic quiescence of the primary disease.

Table 573.2 Characteristics of Children with Incident End-Stage Kidney Disease, by Primary Cause of End-Stage Kidney Disease, 2016–2020

PRIMARY CAUSES OF ESKD	%
All Etiologies	100
Primary Glomerular Disease	21.5
Glomerulonephritis (GN) (histologically not examined)	5.4
Focal glomerulosclerosis, focal sclerosing	11.4
Membranous nephropathy	0.4
Membranoproliferative GN (MPGN) type 1, diffuse MPGN	0.4
Dense deposit disease, MPGN type 2	0.3
IgA nephropathy, Berger's disease (proven by immunofluorescence)	0.5
With lesion of rapidly progressive GN	0.8
Other proliferative GN	2.5
Secondary Glomerular Disease	8.3
Systemic lupus erythematosus (SLE nephritis)	2.6
Hemolytic uremic syndrome	1.9
Polyarteritis and other vasculitis	1.5
Associated vasculitis	1.8
CAKUT1	28.1
Congenital obstructive uropathies	10.1
Renal hypoplasia, dysplasia, oligonephronia	15.0
Chronic pyelonephritis, reflux nephropathy	3.0
Cystic/Hereditary/Congenital Diseases	11.9
Polycystic kidneys, adult type (dominant)	0.5
Polycystic, infantile (recessive)	3.0
Medullary cystic disease, including nephronophthisis	1.7
Hereditary nephritis, Alport syndrome	1.2
Cystinosis	1.0
Primary oxalosis	0.4
Congenital nephrotic syndrome	2.0
Other (congenital malformation syndromes)	1.9
Tubulointerstitial Diseases	4.9
Chronic interstitial nephritis	2.3
Acute interstitial nephritis	0.4
Tubular necrosis	2.1
Transplant Complications	1.5
Other transplant complication	1.4
Diabetes	0.6
Neoplasms/Tumors	0.8
Renal tumor	0.7
Hypertensive/Large Vessel Disease	1.6
Renal artery stenosis	0.3
Renal artery occlusion	1.2
Miscellaneous Conditions	14.0
Acquired obstructive uropathy	4.5
Unspecified with renal failure	2.3
Traumatic or surgical loss of kidney(s)	1.1
Other renal disorders	5.1
Nephropathy caused by other agents	0.9
Etiology Uncertain	4.0
Etiology Missing	2.9

IgA, Immunoglobulin A; CAKUT, congenital anomalies of the kidney and urinary tract. Modified from the United States Renal Data System. 2022 *USRDS* Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2022. Table 8.1. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/8-esrd-among-children-and-adolescents.

In children, dialysis may be required before transplantation to optimize the nutritional and metabolic conditions, allow for quiescence of an underlying autoimmune disorder, achieve an appropriate size, or keep a patient stable until a suitable donor is available. Although successful transplantation with an adult-sized kidney has occurred in children <10 kg and <6 months of age, recipients usually must weigh at least 8-10 kg to minimize the risk for vascular thrombosis and accommodate an adult-size kidney. This may require a period of dialysis support until the child is 12-18 months of age.

Preemptive transplantation (i.e., transplantation without prior dialysis) accounts for ~25% of all pediatric renal transplants. It is the preferred approach when possible because of a small but incremental decrease in patient and allograft survival for every year spent on dialysis before transplant. Preemptive renal transplantation can and should therefore be considered in any child with stage 4 or 5 CKD who is likely to require dialysis within 6-12 months and/or has evidence of the adverse effects of CKD on their health or neurocognitive development. This requires early referral to a transplant center for evaluation of the candidate and potential donors. The transplant team must work with the recipient and caregivers to determine the optimal time for transplantation considering the risks and benefits posed to the recipient.

CHARACTERISTICS OF KIDNEY DONORS AND RECIPIENTS

Approximately 30–40% of pediatric kidney transplants come from **living donors.** Because the Organ Procurement and Transplantation Network (OPTN) gives preference to children waiting for a **deceased-donor** renal transplant, children have a higher rate of transplantation than adults. In 2020, children less than 17 years of age on dialysis were transplanted at a rate of 43.7 transplants per 100 patient-years (29.9 deceased donor, 13.8 living donor), whereas adults were transplanted at a rate of 8.3 transplant per 100 patient-years. The current allocation policy was implemented to allocate priority to children based on projected organ survival using the **Kidney Donor Profile Index (KDPI),** which computes the projected allograft survival from 12 important donor characteristics. Under this system, the top 35% of kidneys (KDPI <35%) are preferentially allocated to children. Additional factors that determine the allocation include the time on dialysis or since listing (whichever is longest), a zero human leukocyte antigen (HLA)-antigen mismatch, calculated panel-reactive antibody (cPRA), prior living donor, and 0 or 1 HLA-DR (HLA–antigen D–related) mismatch. In 2021, a new allocation system was implemented based on a 250-nautical mile radius rather than allocation based on local organ procurement organizations, and children were given even higher priority on the wait-list. Because of such policies, the time on the wait-list for children is shorter than that for adults. Median wait time is approximately 7-8 months for children nationally compared with 4-5 years or more for adults.

EVALUATION AND PREPARING FOR KIDNEY TRANSPLANTATION

A comprehensive transplant evaluation includes a transplant surgeon, nephrologist, dietitian, social worker, psychologist, pharmacist, financial counselor, pretransplant nurse coordinator, and anesthesiologist. A urologist familiar with transplantation is also essential for patients with lower urinary tract anomalies. Important considerations for the transplant evaluation include considering the primary diagnosis and risk of recurrence; ensuring an adequate lower urinary tract for drainage of the transplanted kidney; diagnosing and treating infections; the presence of cardiovascular disease, anemia, and other sequelae of ESKD; and preparing the patient with immunizations before starting lifelong immunosuppression.

Understanding the primary renal disease is essential before kidney transplantation. For instance, a number of primary renal diseases can recur in a transplanted kidney, but this is not a contraindication to transplantation. Recurrent disease accounts for graft loss in almost 7% of primary transplantations and 10% of repeat transplants. **Primary focal segmental glomerulosclerosis (FSGS)** is known to recur in 30–60% of cases and substantially decreases allograft survival. Because **primary hyperoxaluria** is caused by enzymatic defects in the liver, traditionally kidney transplantation has been accompanied by liver transplantation to prevent recurrent disease in the kidney allograft. However, advancements in pharmacotherapy have led to development of **lumasiran**, the first medication approved by the U.S.

Food and Drug Administration (FDA) to treat primary hyperoxaluria. It is not yet known how these medications will affect progression to ESKD in children and/or the need for liver transplantation. Primary **membranoproliferative glomerulonephritis (MPGN)** carries a high risk of disease recurrence (>50%) and decreased allograft survival. Attempts to classify MPGN into immune vs complement-mediated disease may facilitate research that provides insight into prognosis and options for prevention and treatment, but data are still limited. Histologic recurrence with mesangial immunoglobulin (Ig) A deposits is common and occurs in about half of the patients with **IgA nephropathy** and in approximately 30% of patients with **IgA vasculitis** (formerly Henoch-Schönlein purpura), yet it may not necessarily lead to premature allograft failure. **Congenital nephrotic syndrome** rarely recurs after transplantation, although patients can develop **antinephrin antibodies** and present with nephrotic syndrome. **Membranous nephropathy** occurs very rarely in children. The recurrence rate after kidney transplantation for patients who have been treated for **Wilms tumor** is approximately 13%. Although **Alport syndrome** does not recur following transplantation, approximately 3–4% of patients with Alport syndrome can develop de novo **anti–glomerular basement membrane (anti-GBM) glomerulonephritis** that may lead to graft loss. Certain forms of **complement-mediated thrombotic microangiopathy (TMA)** (commonly referred to as **atypical hemolytic uremic syndrome**) caused by inherited defects in complement regulation can recur posttransplant with devastating consequences for the new allograft. These conditions must be evaluated with genetic testing and analysis of the complement system before transplant so appropriate monitoring and therapy with complement inhibition can be applied to prevent recurrent disease.

Due to the high risk of developing Wilms tumor, patients with **Denys-Drash syndrome** should undergo bilateral nephrectomy before transplantation. Other indications for unilateral or bilateral native nephrectomies include hyposthenuria with polyuria, significant proteinuria leading to coagulopathy, recurrent infection of the native kidneys, and severe hypertension resistant to medical management. Nephrectomies are also indicated in cases such as **polycystic kidney disease,** where the native kidneys may become so large that they cause feeding intolerability in infants or prevent space for a transplanted kidney. Finally, it is important to perform bilateral native nephrectomy or ureteral ligation in patients with **primary FSGS** who produce significant amounts of urine protein to allow for surveillance of proteinuria and early identification and treatment of **recurrent FSGS.**

Urologic problems, such as **vesicoureteral reflux, posterior urethral valves,** and/or abnormal bladders as seen in **Eagle-Barrett syndrome**, should be addressed before surgery. Malformations and voiding abnormalities (e.g., neurogenic bladder, bladder dyssynergia, remnant posterior urethral valves, and urethral strictures) should be identified and repaired if possible. Children with urologic disease and renal dysplasia often require multiple operations to optimize the urinary tract anatomy and function. Such procedures include ureteric reimplantation to correct vesicoureteral reflux, bladder augmentation or reconstruction, urinary diversion (vesicostomy, ureterostomy, ileal conduit, continent appendicovesicostomy), and excision of ureteroceles. Good outcomes have been achieved in posterior urethral valve bladders by following a staged procedure of initial valve resection and bladder rehabilitation by a process of regimented double voiding and/or bladder cycling before transplantation. Following transplantation, bladder function in these patients should be followed for the long term because they can become less compliant over time and lead to premature failure of the transplanted allograft.

A comprehensive nutritional assessment should be performed to ensure that an optimal nutritional status is achieved before transplant. Many children with ESKD require nutritional supplements to provide them with sufficient protein and calories. Infants and young children on dialysis often require nasogastric or gastrostomy tube feedings to overcome decreased oral intake from nausea and anorexia due to uremia.

Bone disease should be evaluated for and bone health optimized before transplantation. Uncontrolled secondary hyperparathyroidism may lead to urinary phosphate wasting, hypercalcemia, hypercalciuria, and/or nephrolithiasis posttransplant. A high calcium phosphorus product before transplantation leads to vascular stiffness and calcifications, increasing the risk for cardiovascular disease and difficult-to-control hypertension in the perioperative and posttransplant period.

In the United States, >25% of the deaths in children on maintenance dialysis are a result of cardiovascular disease. Cardiac death is the leading cause of mortality in young adults after transplant in childhood. Therefore evaluation of cardiac function, including echocardiography and electrocardiography, is required before kidney transplantation to ensure sufficient cardiac function to tolerate the large fluid load that accompanies kidney transplantation. Hypertension is common in ESKD and should be treated before transplant. If medical management is insufficient, bilateral nephrectomy may be considered to control the hyperreninemic response from the failing kidneys. Finally, patients with a history of obstructive uropathy and oligohydramnios in utero who survive to kidney transplant may have undiagnosed/unrecognized pulmonary hypertension, which should be evaluated before transplantation.

Anemia needs to be treated before transplantation. Most patients receive erythropoietin, folate, and iron to maintain goals for hemoglobin levels between 11 and 13 g/dL. Blood transfusions should be avoided if possible due to concerns about sensitizing the patient to HLAs before transplant. If a blood transfusion is required, patients should receive leukoreduced red blood cells.

Evaluation for hypercoagulable states is important before renal transplantation because venous thrombosis is an important cause of graft failure. Risk factors for graft thrombosis include history of prior thrombosis, surgical technique, perfusion and reperfusion injury of the graft, young donor age (<6 years), young recipient (<5 years), cold ischemia time >24 hours, arterial hypotension, prior history of peritoneal dialysis, and/or hypoperfusion of an adult allograft transplanted into a small child. Particularly in the young recipient, there must be an evaluation for thrombosis of the iliac vessels and inferior vena cava, especially if there is a history of previous surgery or central line placement. Children who have large protein losses, such as from nephrotic syndrome and/or peritoneal dialysis, can be at an increased risk for thrombosis because of protein loss, such as protein S, protein C, and antithrombin III. Doppler ultrasound, CT angiography, and MR angiography have all been used to evaluate vessels. To minimize the risk of contrast-induced nephropathy associated with CT contrast, patients with advanced CKD or ESKD not yet on dialysis should receive intravenous hydration before and after the study and acidosis should be corrected before giving contrast medium. While MR angiography has traditionally been avoided in patients with CKD or ESKD because of the risk of nephrogenic systemic fibrosis from early forms of gadolinium, the more recent broad availability of newer, more stable gadolinium preparations makes contrast-enhanced MRI a valid and reasonably safe option. Collaboration between radiology and nephrology is important when determining which gadolinium agents to use and when contrast MRI is appropriate in children with CKD and ESKD.

Infections must be identified, prevented, and treated before transplantation. Infectious disease screening includes obtaining a complete history of the following: current or previous infections, all vaccinations, any occupational risks among family members (e.g., healthcare worker), household or other contacts with treatment for tuberculosis, travel within the past 2 years or significant time spent in another country, bacille Calmette-Guérin administration, animal and/or insect exposure, sexual activity, and consumption of high-risk foods such as unpasteurized products. Screening includes a tuberculosis skin test (purified protein derivative) or interferon gamma release assay, cytomegalovirus IgG, Epstein-Barr virus (EBV) antibody panel, varicella titer, measles antibody, hepatitis B serologies, hepatitis C antibody, HIV, and toxoplasmosis. Additional testing for patients who live in or have visited endemic areas might include *Coccidioides* immunodiffusion, serology for *Strongyloides,* and/or antibody for *Histoplasma* antibody. Sexually active patients should also be screened for syphilis, gonorrhea, and *Chlamydia.*

It is recommended that all immunizations be current before transplantation. All live vaccines (measles, mumps, rubella [MMR] and varicella) should be given before transplantation, and antibody titers should be checked for a response because these vaccines should not be given to immunosuppressed patients. MMR may be given as early as 6 months of age. Inhaled (live-attenuated virus) influenza vaccine should not be given to transplant patients, family members, or healthcare providers.

Psychiatric evaluation should be performed before transplantation to evaluate the ability of patients and families to cope with the substantial stressors that accompany caring for a child with a kidney transplant. This evaluation should include screening for depression, substance abuse, and adherence so that problems can be identified and managed before kidney transplantation. If nonadherence is identified or anticipated, interventions should be in place before transplantation.

The ABO blood type must be confirmed twice before a patient is listed for kidney transplantation. Donors and recipients are currently matched for HLA-A, HLA-B, and HLA-DR antigens. In general, better matched organs have improved survival times following kidney transplantation. Matching at the DR locus appears to be especially advantageous, though in the modern era of immunosuppression, successful six-antigen mismatched transplants are performed routinely. All patients must be screened for preformed anti-HLA antibodies before kidney transplantation. The most common, sensitive, and specific method uses flow cytometry and single HLA-antigen beads. In this manner, a patient's PRA can be assessed and is reported as the percentage of the population against which a recipient has anti-HLA antibodies. Patients can become sensitized by a prior transplant, blood transfusions, and/or pregnancy. Highly sensitized patients (PRA >80%) may undergo desensitization with plasmapheresis, anti-CD 20 antibody, and/or proteasome inhibitors to expand the donor pool from which they can safely receive an organ.

IMMUNOSUPPRESSION

Most pediatric kidney transplant centers employ induction immunosuppression at the time of transplant followed by lifelong maintenance immunosuppression with a calcineurin inhibitor and an antiproliferative agent with or without steroids.

Induction Therapy

Induction therapy is used in nearly all pediatric renal transplants to prevent early acute rejection. The OPTN Scientific Registry of Transplant Recipients (OPTN/SRTR) 2020 Annual Report indicates that 60% of patients receive T-cell–depleting induction therapy (rabbit antithymocyte globulin). Use of an interleukin (IL)-2 receptor antagonist (basiliximab) has been stable at between 30% and 40% for the past 5 years, and the rates of no induction therapy have declined to below 10%.

T-Cell Antibodies

Antithymocyte globulin is comprised of rabbit- or horse-derived polyclonal antibodies against human T-lymphocyte antigens that results in a rapid depletion of T lymphocytes. The infusion is generally started in the operating room before reperfusion of the transplant kidney. Most centers use this for standard induction therapy, but some limit its use to induction of sensitized high-risk patients or patients who have concerns for delayed graft function and want to avoid high calcineurin inhibitor levels in the early postoperative period. The standard dosage is 1.5 mg/kg/dose for three to five doses, with daily monitoring of lymphocyte, neutrophil, and platelet counts. Some centers monitor $CD3^+$ subsets and hold the dose if the $CD3^+$ count is below 20 cells/mm^3.

Interleukin-2 Receptor Antibodies

Basiliximab is currently the only monoclonal anti-CD25 antibody on the market. This chimeric (murine/human) anti-CD25 antibody prevents T-cell proliferation but does not cause T-cell depletion. Basiliximab is given in two doses of 10 mg for patients <35 kg and 20 mg for patients ≥35 kg. The first dose should be given within 2 hours before the transplant surgery and the second dose on day 4. Patients tend to tolerate IL-2 receptor antagonists well with few side effects.

Other Induction Therapies

Alemtuzumab (Campath-1H) is a monoclonal antibody against CD52 present on T and B cells, monocytes, and natural killer cells. Some centers have used this induction antibody in steroid and calcineurin inhibitor-sparing protocols, but pediatric data are limited as has been its use.

Other induction therapies for highly sensitized patients include targeting B cells and/or removing neutralizing antibodies by using rituximab against the CD20 epitope on early-lineage and intermediate-lineage B cells, proteasome inhibitors, and plasmapheresis and/or high-dose intravenous immunoglobulin for removing donor-specific antibodies.

Maintenance Immunosuppression

Lifelong maintenance immunosuppression is required in nearly all patients following kidney transplantation. The most common regimens include a calcineurin inhibitor (predominantly tacrolimus vs cyclosporine) and an antiproliferative agent (predominantly mycophenolate mofetil [MMF] vs azathioprine) with or without corticosteroids. The mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus are sometimes used in place of the calcineurin inhibitor or antiproliferative agent. The rationale for combination therapy in children is to provide effective immunosuppression while minimizing the toxicity of any single drug.

Calcineurin Inhibitors

Despite the search for immunosuppression regimens that minimize calcineurin inhibitor exposure, **tacrolimus** remains the centerpiece of maintenance immunosuppression for most pediatric patients in North America. According to OPTN/SRTR in 2020, >90% of children in the United States were placed on tacrolimus-based immunosuppression at the time of transplant. The increasing use of tacrolimus in place of **cyclosporine** can be attributed to studies demonstrating better efficacy (fewer rejections and less reliance on steroids) and less severe cosmetic side effects, such as hypertrichosis, gingival hyperplasia, and coarsening of facial features. This is especially relevant for adolescents for whom unwanted cosmetic side effects can become a barrier to immunosuppression adherence. Tacrolimus also appears to cause less dyslipidemia, though other side effects such as **new-onset diabetes after transplant (NODAT),** tremor, seizure, alopecia, and sleep disturbance seem to be more common in patients treated with tacrolimus. Despite the nearly complete replacement of cyclosporine with tacrolimus, there are select cases when cyclosporine is the preferred agent (e.g., to treat posttransplant recurrence of FSGS or conversion therapy in patients who develop NODAT).

Unfortunately, both calcineurin inhibitors have a narrow therapeutic index and can cause acute and chronic kidney injury. Additionally, many foods and drugs interact with the calcineurin inhibitor metabolism, requiring frequent therapeutic drug monitoring. A usual starting dose of tacrolimus is 0.1-0.15 mg/kg twice a day on the day of the transplant, targeting trough levels above 10 ng/mL for the first month and then tapering down to trough levels of 4-8 ng/mL by 6 months. Patients with CYP3A5 expression (80–90% of patients from African descent vs 20–30% of patients with Caucasian ancestry) often require doses nearly twice as high. Pharmacogenetic testing of CYP3A5 polymorphisms is available and may assist with personalized dosing. The recent development of long-acting tacrolimus preparations (Envarsus XR and Astagraf XL) have provided the opportunity for a simplified, once daily medication regimen. Most long-term immunosuppressive regimens attempt to limit calcineurin inhibitor dosing as much as possible, and the search for calcineurin inhibitor–sparing drug regimens remains an area of intense research.

Antiproliferative Agents

Most immunosuppression regimens for children following kidney transplantation include an antiproliferative agent. **MMF** is the

morpholinoethyl ester prodrug of mycophenolic acid, an inhibitor of de novo purine synthesis, and is part of the initial maintenance immunosuppression regimen in at least two thirds of U.S. pediatric renal transplant recipients. The absence of nephrotoxicity, cardiovascular risk (hypertension, dyslipidemia), and hepatotoxicity make it an attractive option for immunosuppression, and the fact that it has greater efficacy than azathioprine has enabled the use of lower doses of corticosteroids and/or calcineurin inhibitors. Primary toxicities include diarrhea and upset stomach, as well as leukopenia and anemia, affecting up to 40% of patients. These side effects are often transient and can be treated with a temporary dosage reduction, but persistent dose reductions have been associated with an increased risk of rejection. MMF is also associated with a high risk for birth defects, so its use in adolescent females necessitates two forms of birth control and regular pregnancy screening. The usual dose of MMF is 600 mg/m^2 in patients treated with cyclosporine. MMF metabolism is slower in patients treated concomitantly with tacrolimus, allowing for lower doses (450 mg/m^2) to be used.

Azathioprine, an analog of **6-mercaptopurine**, is an alternative to MMF that also inhibits de novo purine synthesis and contributes to cell cycle arrest. It was the first medication approved for immunosuppression in kidney transplantation, yet in the past 2 decades, its use has declined because of the advent of newer immunosuppressive medications with purported greater efficacy. It is inexpensive and, unlike MMF, it can be administered once daily, so it is an attractive alternative for patients who struggle to take twice-daily medications. Usual dosage is 1.5-3 mg/kg once daily. Bone marrow suppression is the primary toxicity, but gastrointestinal side effects are less common than with MMF, with the exception of pancreatitis, which has rarely been reported. Unlike MMF, it is not associated with birth defects and is an important alternative in pregnant patients. Enteric-coated mycophenolic acid is another alternative to MMF that may decrease upper gastrointestinal side effects in some patients.

Mammalian Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors (sirolimus more commonly than everolimus) are used primarily as adjunctive immunosuppression in combination with MMF to avoid tacrolimus toxicity or with tacrolimus and MMF to spare steroids. However, they are used in only 5–10% of pediatric kidney transplant recipients 1 year posttransplant, perhaps due to evidence suggesting a high rate of donor-specific antibodies and antibody-mediated rejection (AMR) in patients taking mTOR inhibitors. Other toxicities, including a high rate of aphthous ulcers, dyslipidemia, poor wound healing, proteinuria, and diarrhea, have limited their use.

Corticosteroids

Corticosteroids remain integral to most immunosuppressive protocols despite their multifaceted toxicities. According to the 2020 OPTN/SRTR report, 54% of patients are treated with steroids at the time of transplant. The adverse effects of steroids are especially pronounced in children, for whom retarded skeletal growth, hypertension, obesity, diabetes mellitus, hyperlipidemia, osteopenia, and aseptic necrosis of bone (particularly the femoral heads) can have dire long-term consequences. Cosmetic side effects, such as cushingoid facies and acne, also become barriers to adolescents taking their medication. For these reasons, steroid-based regimens in children seek to minimize steroid exposure by starting with high-dose steroids as induction therapy and tapering down over several months to a lowest dose of 5-10 mg or 0.1 mg/kg daily. Other protocols call for a more rapid steroid taper lasting from 1 week to several months before stopping them altogether.

Several well-designed randomized controlled trials in children and adults have demonstrated that complete steroid avoidance can be safely achieved in patients with a low immunologic risk by using induction therapy with dual-maintenance immunosuppression comprised of tacrolimus and MMF. In general, steroid avoidance is associated with higher rates of rejection but also carries significant benefits for growth, hypertension, and dyslipidemia with no decrease in long-term allograft survival. Importantly, this approach appears to be safe and without increases in the generation of donor-specific antibody or histologic injury. Despite this evidence, data from the OPTN network suggest that steroid use is largely dependent on the center where the transplant is performed rather than the characteristics of the patient.

Other Agents

Belatacept is a fusion protein composed of the Fc fragment of a human IgG_1 linked to the extracellular domain of CTLA-4 (a molecule crucial for T-cell costimulation), which selectively blocks the process of T-cell activation. Belatacept is attractive for maintenance immunosuppression because it is a quick monthly infusion rather than a daily oral medication, and it does not have many of the untoward side effects associated with calcineurin inhibitors, including and especially nephrotoxicity. Adult studies of belatacept have demonstrated similar rejection rates but significantly improved kidney function up to 10 years following kidney transplantation compared with cyclosporine. Unfortunately, there is an unacceptably high rate of **posttransplant lymphoproliferative disorder (PTLD)** in EBV-naïve patients, which are most of the children receiving a kidney transplant.

FLUID MANAGEMENT IN INFANTS AND SMALL CHILDREN AFTER KIDNEY TRANSPLANTATION

Maintenance of adequate blood flow to an adult-sized kidney in an infant or small child is crucial to avoid acute tubular necrosis (ATN) and graft loss from vascular thrombosis. The recipient aortic blood flow early after transplantation of an adult-size kidney more than doubles from the pretransplantation aortic blood flow. The maximum blood flow that can be obtained in an adult-size kidney transplanted into a small child is approximately 65% of what was in the donor. Low blood flow states, such as those with hypovolemia or hypotension, increase the risk for ATN, graft thrombosis, and graft nonfunction. Thus, in the postoperative period, patients are maintained on high fluid volumes.

Close attention is paid to the blood pressure and hydration status in the operating room in an attempt to reduce the incidence of delayed graft function. Typically, a central venous catheter is inserted to monitor the central venous pressure throughout the operation. A central venous pressure of 12-15 cm H_2O should be achieved before removing the vascular clamps; a higher central venous pressure may be desirable in the case of a small infant receiving an adult-size kidney. Dopamine may be started in the operating room and continued for 24-48 hours postoperatively to maintain a mean arterial blood pressure (MAP) >55 mm Hg. A blood transfusion with packed red blood cells may be required in very small recipients because the hemoglobin can drop as a result of sequestration of approximately 150-250 mL of blood in the transplanted kidney. Because an adult kidney transplanted into a small child can produce enormous amounts of urine, a fluid strategy that provides a constant rate for insensible losses (D10W at a rate of 400 mL/m^2/day) and urine replacements helps to ensure adequate hydration of the adult kidney. Some transplant centers continue to provide infants with aggressive fluid management by nasogastric or gastrostomy tube feedings of at least 2,500 mL/m^2/day for up to 6 months following transplant if the child is unable to take in sufficient volume by mouth.

REJECTION OF KIDNEY TRANSPLANT

Hyperacute rejection, caused by preformed antibodies against the donor HLA, ABO, or other antigens, occurs immediately on reperfusion of the allograft. The practice of prospective cross matching using complement-dependent cytotoxicity has virtually eliminated hyperacute rejection.

Acute T-cell-mediated rejection (TCMR) must be identified and treated promptly, although this may not be straightforward in the very young transplant recipient. Because most small children receive adult-size kidneys with a large renal reserve compared with their body mass, significant allograft dysfunction may be present with little or no increase in serum creatinine. Therefore even subtle findings such as hypertension or new proteinuria can indicate acute TCMR and must be investigated. Late diagnosis and treatment of rejection are associated with a higher incidence of resistant rejections and graft loss. Most cases of acute TCMR can be treated if detected early by using a short course (3-5 days) of high-dose intravenous steroids

(10-30 mg/kg) followed by an oral steroid taper over the next several weeks and either increased maintenance immunosuppression or improved adherence, whichever is most appropriate. Steroid-resistant or high-grade rejection can be treated with thymoglobulin (1.5 mg/kg/day) for 7-14 days, high-dose tacrolimus (trough levels >20 ng/dL for 1-2 weeks), or local allograft irradiation. Following treatment for rejection, it is important to consider 3-12 months of prophylaxis with trimethoprim/sulfamethoxazole to prevent *Pneumocystis jirovecii* pneumonia (PJP pneumonia), valganciclovir/valacyclovir to prevent cytomegalovirus/herpes reactivation, and nystatin or fluconazole to prevent oral candidiasis.

Active AMR consisting of anti-HLA donor-specific antibodies is an important cause of kidney function decline and allograft loss. It can present acutely in the few weeks following transplantation in previously sensitized patients or may develop chronically due to inadequate immunosuppression or poor adherence. Unlike acute TCMR, acute AMR is much more difficult to treat and may require plasmapheresis, intravenous immunoglobulin (IVIG), anti-CD20 antibody infusions, and/or proteasome inhibitors. Treatment is most likely to be successful if initiated within a few months of identifying new donor-specific antibodies.

Chronic rejection (T-cell mediated or antibody mediated) is the leading cause of graft loss. Children often have a gradual decline in their renal function and often have fixed proteinuria and hypertension. Despite initial excitement about the potential of MMF and sirolimus mitigating chronic graft injury, this has not translated readily into observable clinical benefits. Chronic TCMR, chronic AMR, and the impact of non-HLA antibodies are areas of active investigation.

Kidney Biopsy

Kidney biopsy is the gold standard for the diagnosis of TCMR or AMR. Despite attempts to develop noninvasive biomarker panels, none has proven sensitive enough to rule out rejection. Many centers perform **surveillance biopsies** at specific time points following transplantation to detect **subclinical rejection**, which has been reported in <10% of such surveillance biopsies.

GRAFT SURVIVAL OF KIDNEYS

Survival rates for live-donor kidney allografts are superior to those for deceased-donor allografts. Living-donor kidneys generally have fewer HLA mismatches, lower cold ischemia time, and require less immunosuppression than deceased-donor kidneys. Furthermore, deceased-donor transplant requires children to wait several weeks to a few years on the deceased-donor wait-list before receiving an organ. The OPTN/SRTR 2021 annual report showed that the death-censored, 5-year allograft survival rate was 85.2% for deceased-donor kidney transplants performed in 2014–2016, whereas the death-censored, 5-year allograft survival rate for living-donor transplants was 93.1% over the same time period. For these reasons and because it expands the donor pool, living donation should be advocated at every opportunity.

Children <10 years of age have the best long-term graft and patient survival rates of all age-groups, and adolescents and young adults have the worst. Among patients with at least 1 year of graft function, graft failure rates are stable at around 1.4 per 100 person-years until 10 years of age, when rates increase, peaking at a maximum of 6.3 per 100 person-years at age 19 years, regardless of the age at transplantation. A variety of factors likely account for such poor outcomes in adolescents and young adults, including the patient's changing physiology, a transition from pediatric to adult care, and a greater number of barriers to taking immunosuppressives.

COMPLICATIONS OF IMMUNOSUPPRESSION

Since the mid-1990s, the incidence of acute rejection has decreased, but the incidence of infection after transplantation has increased.

Pneumonia and urinary tract infection are the most common post-transplant bacterial infections. Urinary tract infections can progress rapidly to urosepsis and may be confused with episodes of acute rejection. Trimethoprim-sulfamethoxazole is used for urinary tract infection antibiotic prophylaxis as well as PJP prophylaxis for 3-6 months after transplant (see Chapter 290).

The herpesviruses (cytomegalovirus, herpesvirus, varicella-zoster virus, and EBV) pose a special problem in view of their common occurrences in childhood (see Chapters 299-302). Many young children have not yet been exposed to these viruses, and because they lack protective immunity, their predisposition to serious primary infection is high. The incidence of cytomegalovirus seropositivity is approximately 30% in children >5 years of age and rises to approximately 60% in teenagers. Thus the younger child is at a greater potential risk for serious infection when a cytomegalovirus-positive donor kidney is transplanted. About half of children are seronegative for EBV; most of them will become infected shortly after transplant. Most EBV infections are clinically silent but put transplant recipients at risk for PTLD in the presence of immunosuppression. The incidence of these infections is higher in children who receive antibody induction therapy and after treatment of acute rejection. Antiviral prophylaxis with ganciclovir or valganciclovir for 3-12 months after transplantation, especially in the higher-risk groups (recipient-negative, donor-positive), has been effective in reducing the incidence of clinical cytomegalovirus disease. Serial surveillance for these viruses by quantitative polymerase chain reaction (PCR) for the viral load in the peripheral blood has also allowed educated minimization of immunosuppression with a resultant reduction in the viral burden. It is important to monitor for PTLD with routine examinations for lymphadenopathy, hepatosplenomegaly, and EBV screening.

Polyomavirus nephropathy is an important cause of allograft dysfunction; almost 30% of children have BK viruria (see Chapter 321), although allograft dysfunction occurs only in a small subset of patients (~5%). Early protocols focusing on screening for BK virus in the urine have proven ineffective at distinguishing patients who will develop BK nephropathy; rather, plasma BK monitoring has become the standard of care. Ultimately, a renal biopsy, with identification of BK virus by immunoperoxidase staining, is required to make the diagnosis of BK virus nephropathy with certainty. Reducing immunosuppression when plasma BK PCR levels start to rise is the main form of therapy. Cidofovir, leflunomide, and IVIG have all been used as adjunctive therapies.

Oral candidiasis is another important infection following kidney transplantation and can be prevented with oral nystatin 4 times daily or fluconazole once daily for the first 3 months after transplant. Careful monitoring of calcineurin inhibitor levels is important when starting or stopping treatment with fluconazole as it interferes with calcineurin inhibitor metabolism.

Pediatric solid organ transplant patients are generally considered to be at increased risk for infections and worse outcomes compared with their nonimmunosuppressed peers. This concern was brought to the forefront during the global COVID-19 pandemic. Despite their immunosuppressed state, studies have not shown that children with a solid organ transplant are at increased risk for complications from COVID-19 infection. Early studies indicate that short-term outcomes from COVID-19 in pediatric kidney transplant recipients are generally favorable, without increased risk of graft loss, respiratory failure, or death compared with nonimmunosuppressed peers. Nonetheless, COVID-19 vaccination is recommended before transplantation to minimize risk of complications and spread.

Hypertension, dyslipidemia, obesity, and posttransplant diabetes mellitus are other complications of immunosuppression and kidney transplantation that have been underrecognized and undertreated. Cardiovascular disease is the primary cause of premature death in young adults who had a kidney transplant in childhood, and uncontrolled blood pressure leads to premature allograft failure. Up to 80% of children have hypertension and up to 60% are uncontrolled despite multiple available therapies. The 24-hour ambulatory blood pressure monitoring (ABPM) is the gold standard for assessing blood pressure control because isolated nocturnal hypertension and masked hypertension are common following kidney transplantation and can only be diagnosed with ABPM. Guidelines for CKD recommend treating blood pressure to achieve a MAP below the 50th percentile for age, gender, and height on ABPM, though recommendations for children with a kidney transplant have not been as aggressive. Blood pressure

should be treated to at least below the 90th percentile for age, gender, and height and below 130/80 mm Hg. Angiotensin-converting enzyme (ACE) inhibitors are the preferred first-line agents in patients with proteinuria; otherwise, either calcium channel blockers or ACE inhibitors can be used with other agents added as needed to achieve blood pressure control.

Although growth improves after transplantation, chronic steroid use does not allow a child to reach their full potential height. The use of recombinant human growth hormone in pediatric renal transplant recipients significantly improves the growth velocity and standard deviation score (SDS). Steroid minimization and withdrawal protocols have demonstrated growth benefits, and the steroid-avoidance data in children show significant catch-up growth at 5 years after transplantation. It is thus likely that with a well-functioning kidney and no maintenance steroids, children might now be able to realize their full height potential.

Malignancy is an important problem following kidney transplantation for children. Lifelong immunosuppression confers at least a twofold lifetime risk of developing cancer for solid-organ transplant recipients compared with the general population. The most common cancer to develop within 10 years following kidney transplantation in children is **PTLD.** It occurs in 1–5% of pediatric kidney transplant recipients and is the most likely cancer to be encountered in childhood. Over the long term, skin cancers (basal cell carcinoma, cutaneous squamous cell carcinoma) are the most common malignancies, with an incidence of close to 15% by 15 years posttransplant and increasing from there. Carcinomas other than skin carcinomas also arise at a rate far higher than in the general population. The prognosis is generally good for most of these malignancies when they are diagnosed early and treated appropriately. Any kidney transplant recipient must be assessed regularly for signs of malignancy and practice preventative measures such as using appropriate sunscreen products.

Developing good adherence behaviors with immunosuppressive medications is one of the most important challenges facing children and adolescents following kidney transplantation. Up to 43% of adolescents display some decreased adherence to their immunosuppressive regimen, which is thought to contribute to decreased allograft survival rates compared with other age-groups. A child's normal development, which includes establishing more independence, spending more time away from home, feeling invincible, and being vulnerable to cosmetic medication side effects, increases the barriers to taking immunosuppression medications. Systems-based approaches, in which clinicians partner with patients to identify and address adherence barriers, are most likely to improve adherence over the long term.

LONG-TERM OUTCOME OF KIDNEY TRANSPLANTATION

With advances in transplant care and treatment modalities and with diligent attention to the pediatric patient's psychosocial, educational, vocational, and developmental rehabilitation, the social and emotional functioning of the child and the child's family appears to return to the same level as before the illness within 1 year of successful transplantation. Renal transplantation leads to improvement in linear growth in children. School function tests improve after renal transplantation. Most patients can reenter school and social activities after a short recovery time of 6-12 weeks following surgery. Surveys of 10-year survivors of pediatric kidney transplants report that most patients consider their health to be good, and they engage in appropriate social, educational, and sexual activities while experiencing a very good to excellent quality of life.

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