Pathophsiology

Disorder of renal system

25-11-2018

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Clinical Manifestations Of Renal Diseases

The clinical manifestations of renal disease can be grouped into reasonably well-defined syndromes. Some are peculiar to glomerular diseases and others are shared by several renal disorders. **Before we list the syndromes, a few terms must be defined :-**

Azotemia is an elevation of blood urea nitrogen and creatinine levels and usually reflects a decreased glomerular filtration rate (GFR). GFR may be decreased as a consequence of intrinsic renal disease or extrarenal causes.

Prerenal azotemia is encountered when there is hypoperfusion of the kidneys, which decreases GFR in the absence of parenchymal damage. **Postrenal azotemia** results when urine flow is obstructed below the level of the kidney. Relief of the obstruction is followed by correction of the azotemia. When azotemia gives rise to clinical manifestations and systemic biochemical abnormalities, it is termed uremia.

Uremia is characterized not only by failure of renal excretory function but also by a host of metabolic and endocrine alterations incident to renal damage.There is, in addition, secondary gastrointestinal (e.g., uremic gastroenteritis); neuromuscular (e.g., peripheral neuropathy); and cardiovascular (e.g., uremic fibrinous pericarditis) involvement

Major renal syndromes:

• **Nephritic syndrome** Nephritic syndrome results from glomerular injury and is dominated by the acute onset of usually grossly visible hematuria (red blood cells and red cell casts in urine), proteinuria of mild to moderate degree, azotemia, edema, and hypertension; it is the classic presentation of acute poststreptococcal glomerulonephritis.

• **Asymptomatic hematuria** or non-nephrotic proteinuria, or a combination of these two, is usually a manifestation of subtle or mild glomerular abnormalities.

• **Rapidly progressive glomerulonephritis** is associated with severe glomerular injury and results in loss of renal function in a few days or weeks. It is manifested by microscopic hematuria, dysmorphic red blood cells and red cell casts in the urine sediment, and mild to moderate proteinuria

• **Acute kidney injury** is dominated by oliguria or anuria (no urine flow), and recent onset of azotemia. It can result from glomerular injury (such as rapidly progessive glomerulonephritis), interstitial injury, vascular injury (such as thrombotic microangiopathy), or acute tubular injury.

• **Chronic kidney disease**, characterized by prolonged symptoms and signs of uremia, is the result of progressive scarring in the kidney from any cause and may culminate in end-stage kidney disease, requiring dialysis or transplantation.

• **Urinary tract infection** is characterized by bacteriuria and pyuria (bacteria and leukocytes in the urine). The infection may be symptomatic or asymptomatic, and it may affect the kidney (pyelonephritis) or the bladder (cystitis) only.

• **Nephrolithiasis** (renal stones) is manifested by renal colic, hematuria (without red cell casts), and recurrent stone formation.

In addition to these renal syndromes, urinary tract obstruction and renal tumors also commonly present with signs and symptoms related to renal dysfunction .

Glomerular Diseases

Mechanisms of Glomerular Injury

• Antibody-mediated immune injury is an important mechanism of glomerular damage, mainly by way of complement- and leukocyte-mediated pathways. Antibodies also may be directly cytotoxic to cells in the glomerulus.

Table 13–1 Glomerular Diseases

Primary Glomerular Diseases
Minimal-change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Acute postinfectious GN
Membranoproliferative GN
IgA nephropathy
Glomerulopathies Secondary to Systemic Diseases
Lupus nephritis (systemic lupus erythematosus)
Diabetic nephropathy
Amyloidosis
GN secondary to multiple myeloma
Goodpasture syndrome
Microscopic polyangiitis
Wegener granulomatosis
Henoch-Schönlein purpura
Bacterial endocarditis–related GN
Thrombotic microangiopathy
Hereditary Disorders
Alport syndrome
Fabry disease
Podocyte/slit-diaphragm protein mutations

GN, glomerulonephritis; IgA, immunoglobulin A.

Mechanisms of Glomerular Injury

• The most common forms of antibody-mediated GN are caused by the formation of immune complexes, whether occurring in situ or by deposition of circulating immune complexes. These immune complexes may contain exogenous (e.g. microbial) circulating antigens or endogenous antigens (e.g. in membranous nephropathy). Immune complexes show a granular pattern of deposition.

• Autoantibodies against components of the GBM are the cause of anti-GBM-antibody–mediated disease, often associated with severe injury.

• Immune complexes and antibodies cause injury by complement activation and leukocyte recruitment, with release of various mediators, and sometimes by direct podocyte damage.

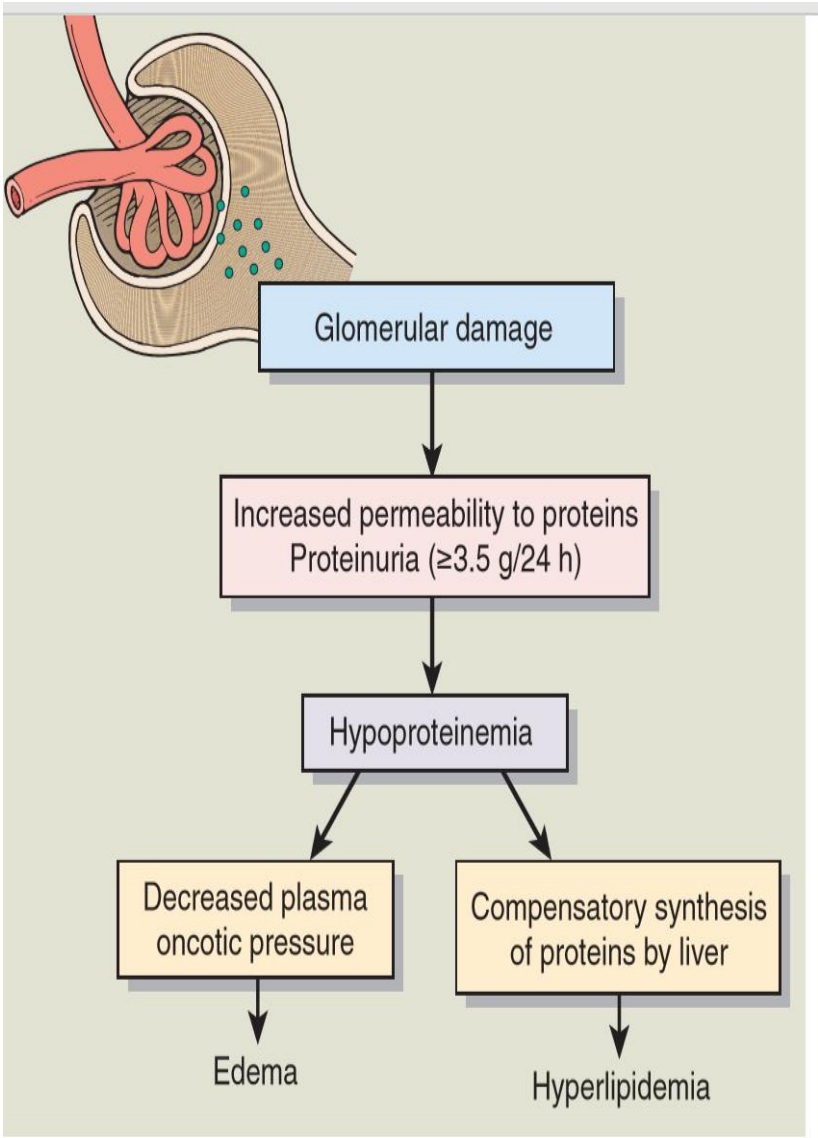
The Nephrotic Syndrome

The nephrotic syndrome refers to a clinical complex that includes

- Massive proteinuria, with daily protein loss in the urine of 3.5 g or more in adults
- Hypoalbuminemia, with plasma albumin levels less than 3 g/dL
- Generalized edema, the most obvious clinical manifestation
- Hyperlipidemia and lipiduria

Pathophysiology of the nephrotic syndrome

The nephrotic syndrome has diverse causes that share a common pathophysiology . In all there is a derangement in the capillary walls of the glomeruli that results in increased permeability to plasma proteins. Any increased permeability resulting from either structural or physicochemical alterations in the GBM allows protein to escape from the plasma into the glomerular filtrate. With long-standing or extremely heavy proteinuria, serum albumin is decreased, resulting in hypoalbuminemia and a drop in plasma colloid osmotic pressure



The resulting decrease in intravascular volume and renal blood flow triggers increased release of renin from renal juxtaglomerular cells. Renin in turn stimulates the angiotensin-aldosterone axis, which promotes the retention of salt and water by the kidney. This tendency is exacerbated by reductions in the cardiac secretion of natriuretic factors. In the face of continuing proteinuria, these alterations further aggravate the edema and if unchecked may lead to the development of generalized edema (termed anasarca). At the onset, there is little or no azotemia, hematuria, or hypertension. The genesis of the hyperlipidemia is more obscure. Presumably, hypoalbuminemia triggers increased synthesis of lipoproteins in the liver or massive proteinuria causes loss of an inhibitor of their synthesis. There is also abnormal transport of circulating lipid particles and impairment of peripheral breakdown of lipoproteins. The lipiduria, in turn, reflects the increased permeability of the GBM to lipoproteins.

The most important of the primary glomerular lesions that characteristically lead to the nephrotic syndrome are focal and segmental glomerulosclerosis and minimal-change disease. The latter is more important in children; the former, in adults. Two other primary lesions, membranous nephropathy and membranoproliferative glomerulonephritis, also commonly produce the nephrotic syndrome.

Table 13–2 Causes of Nephrotic Syndrome

Cause	Prevalence (%)*	
	Children	Adults
Primary Glomerular Disease		
Membranous nephropathy	5	30
Minimal-change disease	65	10
Focal segmental glomerulosclerosis	10	35
Membranoproliferative glomerulonephritis	10	10
IgA nephropathy and others	10	15
Systemic Diseases with Renal Manifestations		
Diabetes mellitus		
Amyloidosis		
Systemic lupus erythematosus		
Ingestion of drugs (gold, penicillamine, "street heroin")		
Infections (malaria, syphilis, hepatitis B, HIV infection)		
Malignancy (carcinoma, melanoma)		
Miscellaneous (bee sting allergy, hereditary nephritis)		

*Approximate prevalence of primary disease is 95% of the cases in children, 60% in adults. Approximate prevalence of systemic disease is 5% of the cases in children, 40% in adults.
HIV, human immunodeficiency virus.

Minimal-Change Disease

Minimal-change disease, a relatively benign disorder, is the most frequent cause of the nephrotic syndrome in children. Characteristically, the glomeruli have a normal appearance by light microscopy but show diffuse effacement of podocyte foot processes when viewed with the electron microscope. Although it may develop at any age, this condition is most common between the ages of 1 and 7 years.

The pathogenesis of proteinuria in minimal-change disease remains to be elucidated. On the basis of some experimental studies, the proteinuria has been attributed to a circulating, possibly T cell–derived, factor that causes podocyte damage and effacement of foot processes.

Clinical Course

The disease manifests with the insidious development of the nephrotic syndrome in an otherwise healthy child. There is no hypertension, and renal function is preserved in most of these patients. The protein loss usually is confined to the smaller plasma proteins, chiefly albumin (selective proteinuria). The prognosis for children with this disorder is good.More than 90% of children respond to a short course of corticosteroid therapy; however, proteinuria recurs in more than two thirds of the initial responders, some of whom become steroid-dependent.Less than 5% develop chronic kidney disease after 25 years, and it is likely that most persons in this subgroup had nephrotic syndrome caused by focal and segmental glomerulosclerosis not detected by biopsy.Because of its responsiveness to therapy in children, minimal-change disease must be differentiated from other causes of the nephrotic syndrome in nonresponders.Adults with this disease also respond to steroid therapy, but the response is slower and relapses are more common.

Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is characterized histologically by sclerosis affecting some but not all glomeruli (focal involvement) and involving only segments of each affected glomerulus (segmental involvement). This histologic picture often is associated with the nephrotic syndrome. FSGS may be primary (idiopathic) or secondary to one of the following conditions:

- In association with other conditions, such as HIV infection (HIV nephropathy)
- As a secondary event in other forms of GN (e.g., IgA nephropathy)
- As a maladaptation to nephron loss
- In inherited or congenital forms.

Pathogenesis

The pathogenesis of primary FSGS is unknown. Some investigators have suggested that FSGS and minimal-change disease are part of a continum and that minimal-change disease may transform into FSGS. In any case, injury to the podocytes is thought to represent the initiating event of primary FSGS. As with minimal-change disease, permeability-increasing factors produced by lymphocytes have been proposed. The deposition of hyaline masses in the glomeruli represents the entrapment of plasma proteins and lipids in foci of injury where sclerosis develops. IgM and complement proteins commonly seen in the lesion are also believed to result from nonspecific entrapment in damaged glomeruli. The recurrence of proteinuria and subsequent FSGS in a renal transplant in some patients who had FSGS, sometimes within 24 hours of transplantation, supports the idea that a circulating mediator is the cause of the podocyte damage in some cases.

Clinical Course

In children it is important to distinguish FSGS as a cause of the nephrotic syndrome from minimal-change disease, because the clinical courses are markedly different. The incidence of hematuria and hypertension is higher in persons with FSGS than in those with minimal-change disease; the FSGSassociated proteinuria is nonselective; and in general the response to corticosteroid therapy is poor. At least 50% of patients with FSGS develop end-stage kidney disease within 10 years of diagnosis. Adults typically fare even less well than children.

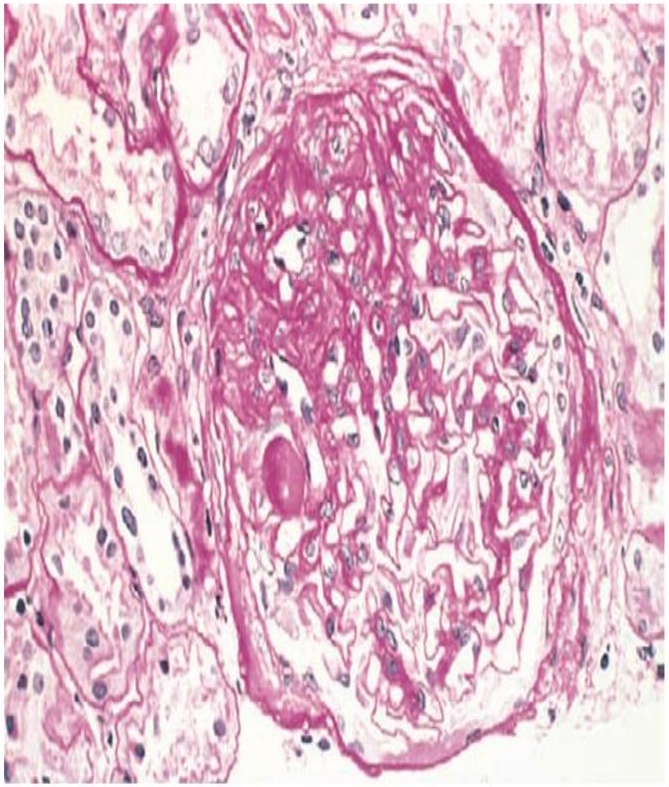


Figure 13–7 High-power view of focal and segmental glomerulosclerosis (periodic acid–Schiff stain), seen as a mass of scarred, obliterated capillary lumens with accumulations of matrix material that has replaced a portion of the glomerulus.

(Courtesy of Dr. H. Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)

Membranous Nephropathy

Membranous nephropathy is a slowly progressive disease, most common between 30 and 60 years of age. It is characterized morphologically by the presence of subepithelial immunoglobulin-containing deposits along the GBM. Early in the disease, the glomeruli may appear normal by light microscopy, but well-developed cases show diffuse thickening of the capillary wall. In about 85% of cases, membranous nephropathy is caused by autoantibodies that cross-react with antigens expressed by podocytes. In the remainder (secondary membranous nephropathy), it occurs secondary to other disorders, including

- Infections (chronic hepatitis B, syphilis, schistosomiasis, malaria)
- Malignant tumors, particularly carcinoma of the lung and colon and melanoma
- Systemic lupus erythematosus and other autoimmune conditions
- Exposure to inorganic salts (gold, mercury)
- Drugs (penicillamine, captopril, nonsteroidal antiinflammatory agents)

Summary

The Nephrotic Syndrome

• The nephrotic syndrome is characterized by proteinuria, which results in hypoalbuminemia and edema.

• Podocyte injury is an underlying mechanism of proteinuria, and may be the result of nonimmune causes (as in minimal- change disease and FSGS) or immune mechanisms (as in membranous nephropathy).

• Minimal-change disease is the most frequent cause of nephrotic syndrome in children; it is manifested by proteinuria and effacement of glomerular foot processes without antibody deposits; the pathogenesis is unknown; the disease responds well to steroid therapy.

• FSGS may be primary (podocyte injury by unknown mechanisms) or secondary (e.g., as a consequence of previous glomerulonephritis, hypertension, or infection such as with HIV); glomeruli show focal and segmental obliteration of capillary lumina, and loss of foot processes; the disease often is resistant to therapy and may progress to end-stage renal disease.

• Membranous nephropathy is caused by an autoimmune response, most often directed against the phospholipase A2 receptor on podocytes; it is characterized by granular subepithelial deposits of antibodies with GBM thickening and loss of foot processes but little or no inflammation; the disease often is resistant to steroid therapy.

Rapidly Progressive Glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome and not a specific etiologic form of GN. It is characterized by progressive loss of renal function, laboratory findings typical of the nephritic syndrome, and often severe oliguria. If untreated, it leads to death from renal failure within a period of weeks to months. The characteristic histologic finding associated with RPGN is the presence of crescents (crescentic GN).

Pathogenesis

Crescentic GN caused by a number of different diseases, some restricted to the kidney and others systemic. Although no single mechanism can explain all cases, there is little doubt that in most cases the glomerular injury is immunologically mediated. The diseases causing crescentic GN may be associated with a known disorder or it may be idiopathic. When the cause can be identified, about 12% of the patients have anti-GBM antibody–mediated crescentic GN with or without lung involvement; 44% have immune complex GN with crescents; and the remaining 44% have pauciimmune crescentic GN. All have severe glomerular injury.

Morphology

The kidneys are enlarged and pale, often with petechial hemorrhages on the cortical surfaces. Glomeruli show segmental necrosis and GBM breaks, with resulting proliferation of the parietal epithelial cells in response to the exudation of plasma proteins and the deposition of fibrin in Bowman's space. These distinctive lesions of proliferation are called crescents owing to their shape as they fill Bowman's space. Crescents are formed both by proliferation of parietal cells and by migration of monocytes/macrophages into Bowman's space .

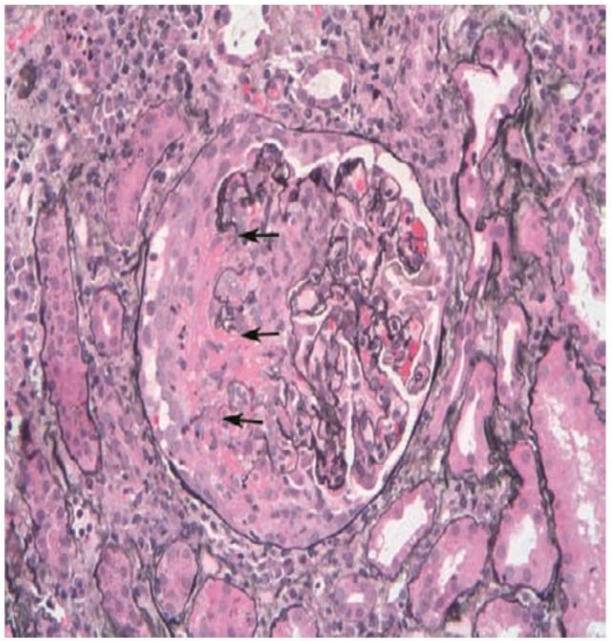


Figure 13–12 Crescentic glomerulonephritis (GN) (Jones silver methenamine stain). Note the areas of necrosis with rupture of capillary loops (*arrows*) and destruction of normal glomerular structures, and the adjacent crescent-shaped mass of proliferating cells and leukocytes filling the urinary space. The segmental distribution of the necrotizing and crescentic GN is typical of ANCA (antineutrophil cytoplasmic antibody)-associated crescentic GN.

Summary

Rapidly Progressive Glomerulonephritis

• RPGN is a clinical entity with features of the nephritic syndrome and rapid loss of renal function.

• RPGN is commonly associated with severe glomerular injury with necrosis and GBM breaks and subsequent proliferation of parietal epithelium (crescents).

• RPGN may be immune-mediated, as when autoantibodies to the GBM develop in anti-GBM antibody disease or when it arises consequent to immune complex deposition; it also can be pauci-immune, associated with antineutrophil cytoplasmic antibodies.

Diseases Affecting Tubules And Interstitium

Acute Pyelonephritis

Acute pyelonephritis, a common suppurative inflammation of the kidney and the renal pelvis, is caused by bacterial infection. It is an important manifestation of urinary tract infection (UTI), which can involve the lower (cystitis, prostatitis, urethritis) or upper (pyelonephritis) urinary tract, or both. As we shall see, the great majority of cases of pyelonephritis are associated with infection of the lower urinary tract. Such infection, however, may remain localized without extending to involve the kidney.

Pathogenesis

The principal causative organisms in acute pyelonephritis are the enteric gram-negative rods. Escherichia coli is by far the most common one. Other important organisms are Proteus, Klebsiella, Enterobacter, and Pseudomonas; these usually are associated with recurrent infections, especially in persons who undergo urinary tract manipulations or have congenital or acquired anomalies of the lower urinary tract .Staphylococci and Streptococcus faecalis also may cause pyelonephritis, but they are uncommon pathogens in this setting. Bacteria can reach the kidneys from the lower urinary tract **(ascending infection)** or through the blood stream **(hematogenous infection)** .

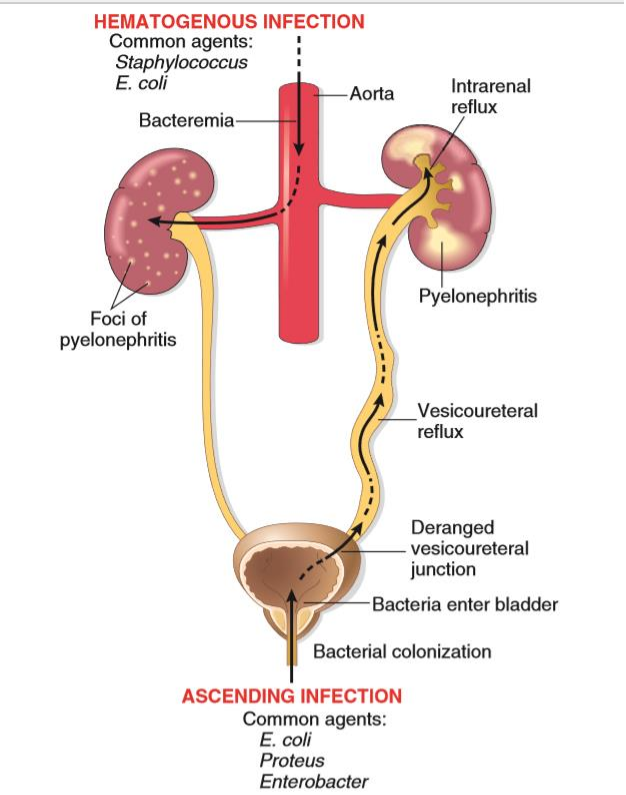


Figure 13–13 Pathways of renal infection. Hematogenous infection results from bacteremic spread. More common is ascending infection, which results from a combination of urinary bladder infection, vesicoureteral reflux, and intrarenal reflux.

Ascending infection from the lower urinary tract is the most important and common route by which the bacteria reach the kidney. Adhesion of bacteria to mucosal surfaces is followed by colonization of the distal urethra (and the introitus in females). Genetically determined properties of both the urothelium and the bacterial pathogens may facilitate adhesion to the urothelial lining by bacterial fimbriae (proteins that attach to receptors on the surface of urothelial cells), conferring susceptibility to infection. The organisms then reach the bladder, by expansive growth of the colonies and by moving against the flow of urine. This may occur during urethral instrumentation, including catheterization and cystoscopy. Although **hematogenous spread** is the far less common of the two, acute pyelonephritis may result from seeding of the kidneys by bacteria in the course of septicemia or infective endocarditis.

In the absence of instrumentation, UTI most commonly affects females. Because of the close proximity of the female urethra to the rectum, colonization by enteric bacteria is favored. Furthermore, the short urethra, and trauma to the urethra during sexual intercourse, facilitate the entry of bacteria into the urinary bladder. Ordinarily, bladder urine is sterile, as a result of the antimicrobial properties of the bladder mucosa and the flushing mechanism associated with periodic voiding of urine. With outflow obstruction or bladder dysfunction, however, the natural defense mechanisms of the bladder are overwhelmed, setting the stage for UTI. In the presence of stasis, bacteria introduced into the bladder can multiply undisturbed, without being flushed out or destroyed by the bladder wall. From the contaminated bladder urine, the bacteria ascend along the ureters to infect the renal pelvis and parenchyma. Accordingly, UTI is particularly frequent among patients with urinary tract obstruction, as may occur with benign prostatic hyperplasia and uterine prolapse.

UTI frequency also is increased in diabetes because of the increased susceptibility to infection and neurogenic bladder dysfunction, which in turn predisposes to stasis. Incompetence of the vesicoureteral orifice, resulting in vesicoureteral reflux (VUR), is an important cause of ascending infection.

The reflux allows bacteria to ascend the ureter into the pelvis. VUR is present in 20% to 40% of young children with UTI, usually as a consequence of a congenital defect that results in incompetence of the ureterovesical valve. VUR also can be acquired in persons with a flaccid bladder resulting from spinal cord injury or with neurogenic bladder dysfunction secondary to diabetes. VUR results in residual urine after voiding in the urinary tract, which favors bacterial growth. Furthermore, VUR affords a ready mechanism by which the infected bladder urine can be propelled up to the renal pelvis and farther into the renal parenchyma through open ducts at the tips of the papillae (intrarenal reflux).

Morphology

One or both kidneys may be involved. The affected kidney may be normal in size or enlarged. Characteristically, discrete, yellowish, raised abscesses are grossly apparent on the renal surface .They may be widely scattered or limited to one region of the kidney, or they may coalesce to form a single large area of suppuration. The characteristic histologic feature of acute pyelonephritis is liquefactive necrosis with abscess formation within the renal parenchyma. In the early stages pus formation (suppuration) is limited to the interstitial tissue, but later abscesses rupture into tubules.

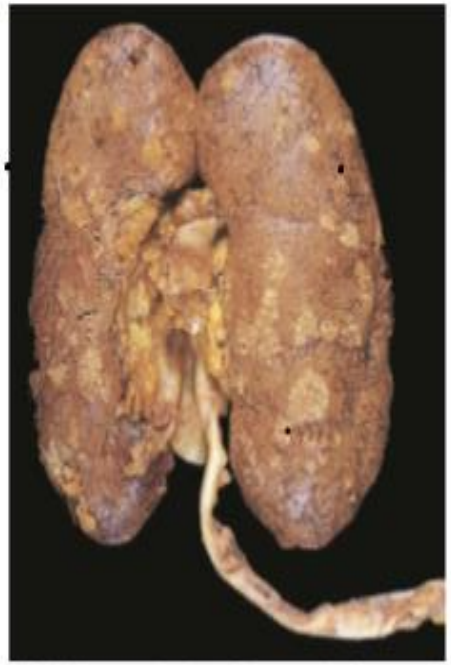


Figure 13–14 Acute pyelonephritis. The cortical surface is studded with focal pale abscesses, more numerous in the upper pole and middle region of the kidney; the lower pole is relatively unaffected. Between the abscesses there is dark congestion of the renal surface.

Diabetic Glomerulosclerosis

Diabetic nephropathy is a major cause of chronic kidney disease and the most common cause of kidney failure treated by renal replacement therapy in the United States and Canada . The lesions of diabetic nephropathy most commonly involve the glomeruli and are associated with three glomerular syndromes: nonnephrotic proteinuria, nephrotic syndrome, and chronic renal failure. Widespread thickening of the glomerular capillary basement membrane occurs in almost all persons with diabetes and can occur without evidence of proteinuria.This is followed by a diffuse increase in mesangial matrix, with mild proliferation of mesangial cells. As the disease progresses, the mesangial cells impinge on the capillary lumen, reducing the surface area for glomerular filtration. In nodular glomerulosclerosis, also known as Kimmelstiel-Wilson syndrome, there is nodular deposition of hyaline in the mesangial portion of the glomerulus. As the sclerotic process progresses in the diffuse and nodular forms of glomerulosclerosis, there is complete obliteration of the glomerulus, with impairment of renal function.

Although **the mechanisms of glomerular change in diabetes are uncertain**, they are thought to represent enhanced or defective synthesis of the glomerular basement membrane and mesangial matrix with inappropriate incorporation of glucose into the noncellular components of these glomerular structures. Alternatively, hemodynamic changes that occur secondary to elevated blood glucose levels may contribute to the initiation and progression of diabetic glomerulosclerosis.It has been hypothesized that elevations in blood glucose produce an increase in GFR and glomerular pressure that leads to enlargement of glomerular capillary pores by a mechanism that is, at least partly, mediated by angiotensin II. This enlargement results in an increase in the protein content of the glomerular filtrate, which in turn requires increased endocytosis of the filtered proteins by tubular endothelial cells, a process that ultimately leads to nephron destruction and progressive deterioration of renal function.

The clinical manifestations of diabetic glomerulosclerosis are closely linked to those of diabetes. The increased GFR that occurs in persons with early alterations in renal function is associated with microalbuminuria, defined as urinary albumin excretion of 30 to 300 mg in 24 hours.5 Microalbuminuria is an important predictor of future diabetic nephropathies.4,19 In many cases, these early changes in glomerular function can be reversed by careful control of blood glucose levels .Inhibition of angiotensin by ACE inhibitors or angiotensin receptor blockers (ARBs) has been shown to have a beneficial effect, possibly by reversing increased glomerular pressure.19 Hypertension and cigarette smoking have been implicated in the progression of diabetic nephropathy. Thus, control of blood pressure (to levels of 130/80 mm Hg or less) and smoking cessation are recommended as primary and secondary prevention strategies in persons with diabetes.

Hypertensive Glomerular Disease

Mild to moderate hypertension causes sclerotic changes in renal arterioles and small arteries, Hypertensive nephropathy is associated with a number of changes in kidney structure and function.The kidneys are smaller than normal and are usually affected bilaterally.5 On histologic examination, there is narrowing of the arterioles and small arteries, caused by thickening and hyalinization of the vessel walls.As the vascular structures thicken and perfusion diminishes, blood flow to the nephron decreases, causing patchy tubular atrophy, interstitial fibrosis, and a variety of changes in glomerular structure and function.Although uncomplicated hyper tensive nephrosclerosis is not usually associated with significant abnormalities in renal function, a few persons may progress to chronic kidney disease.

Drug-Related Nephropathies

Drug-related nephropathies involve functional or structural changes in the kidneys that occur after exposure to a drug. Because of their large blood flow and high filtration pressure, the kidneys are exposed to any substance that is in the blood. The kidneys also are active in the metabolic transformation of drugs and therefore are exposed to a number of toxic metabolites. The tolerance to drugs varies with age and depends on renal function, state of hydration, blood pressure, and the pH of the urine. Elderly persons are particularly susceptible to kidney damage caused by drugs and toxins. The dangers of nephrotoxicity are increased when two or more drugs capable of producing kidney damage are given at the same time. Drugs and toxic substances can damage the kidneys by causing a decrease in renal blood flow, obstructing urine flow, directly damaging tubulointerstitial structures, or producing hypersensitivity reactions.

Acute renal failure

(ARF), which is a common threat to seriously ill persons, represents a rapid decline in kidney function, resulting in an inability to maintain fluid and electrolyte balance and to excrete nitrogenous wastes. Acute renal failure is also called acute kidney injury, because even small decrements in kidney function, changes that are insufficient to be recognized as renal failure, are associated with increased morbidity and mortality. Despite advances in treatment methods, the mortality rate from ARF has not changed substantially since the 1960s. This probably is because ARF is seen more often in older persons than before, and because it frequently is superimposed on other life-threatening conditions, such as trauma, shock,and sepsis. The most common indicator of acute renal failure is azotemia, an accumulation of nitrogenous wastes (urea nitrogen, uric acid, and creatinine) in the blood and a decrease in the glomerular filtration rate (GFR).As a result, excretion of nitrogenous wastes is reduced and fluid and electrolyte balance cannot be maintained.

Types of Acute Renal Failure

■ Acute renal failure is caused by conditions that produce an acute shutdown in renal function.

■ It can result from decreased blood flow to the kidney (prerenal failure), disorders that disrupt the structures ir the kidney (intrinsic or intrarenal failure), or disorders that interfere with the elimination of urine from the kidney (postrenal failure).

■ Acute renal failure, although it causes an accumulation of products normally cleared by the kidney, is a potentially reversible process if the factors causing the condition can be corrected.

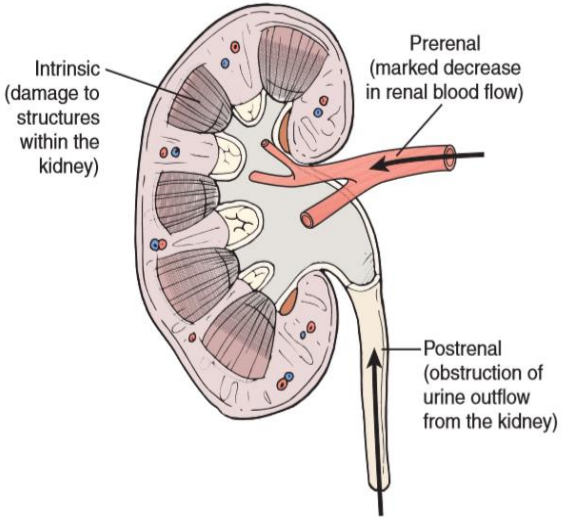


FIGURE 26-1. Types of acute renal failure.

CHART 26-1 Causes of Acute Renal Failure

Prerenal
- Hypovolemia
  - Hemorrhage
  - Dehydration
  - Excessive loss of gastrointestinal tract fluids
  - Excessive loss of fluid due to burn injury
- Decreased vascular filling
  - Anaphylactic shock
  - Septic shock
- Heart failure and cardiogenic shock
- Decreased renal perfusion due to sepsis, vasoactive mediators, drugs, diagnostic agents

Intrinsic or intrarenal
- Acute tubular necrosis
  - Prolonged renal ischemia
  - Exposure to nephrotoxic drugs, heavy metals, and organic solvents
  - Intratubular obstruction resulting from hemoglobinuria, myoglobinuria, myeloma light chains, or uric acid casts
  - Acute renal disease (acute glomerulonephritis, pyelonephritis)

Postrenal
- Bilateral ureteral obstruction
- Bladder outlet obstruction

Chronic Kidney Disease

Chronic kidney disease is the result of progressive scarring resulting from any type of kidney disease. Alterations in the function of remaining initially intact nephrons are ultimately maladaptive and cause further scarring. This eventually results in an end-stage kidney where glomeruli, tubules, interstitium and vessels are sclerosed, regardless of the primary site of injury. Unless the disorder is treated with dialysis or transplantation, death from uremia results.

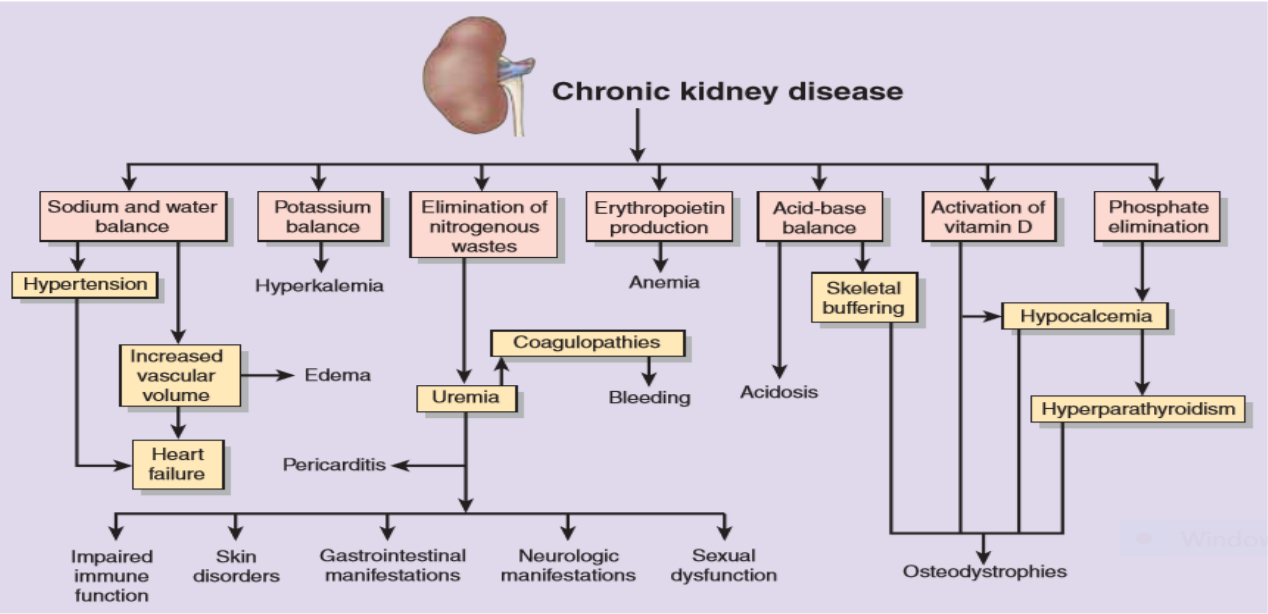


FIGURE 26-4. Mechanisms and manifestations of chronic kidney disease.

Morphology

Classically, the kidneys are symmetrically contracted, and their surfaces are red-brown and diffusely granular when the underlying disorder affects blood vessels or glomeruli. Kidneys damaged by chronic pyelonephritis are typically unevenly involved and have deep scars. Microscopically, the feature common to all cases is advanced scarring of the glomeruli, sometimes to the point of complete sclerosis. This obliteration of the glomeruli is the end point of many diseases, and it is impossible to ascertain from such kidneys the nature of the initial lesion. There is also marked interstitial fibrosis, associated with atrophy and dropout of many of the tubules in the cortex, and diminution and loss of portions of the peritubular capillary network. The small and medium-sized arteries frequently are thick-walled, with narrowed lumina, secondary to hypertension. Lymphocytic (and, rarely, plasma cell) infiltrates are present in the fibrotic interstitial tissue. As damage to all structures progresses, it may become difficult to ascertain whether the primary lesion was glomerular, vascular, tubular, or interstitial. Such markedly damaged kidneys have been designated end stage kidneys.

Clinical Course

Chronic kidney disease may sometimes develop insidiously and be discovered only late in its course, after the onset of renal insufficiency. Frequently, renal disease is first detected with the discovery of proteinuria, hypertension, or azotemia on routine medical examination. Diseasespecific findings may precede development of chronic kidney disease. In patients with glomerular disease resulting in nephrotic syndrome, as the glomeruli undergo sclerotic changes, the avenue for protein loss is progressively closed, and the nephrotic syndrome thus becomes less severe with more advanced disease. Some degree of proteinuria, however, is present in almost all cases. Hypertension is very common, and its effects may dominate the clinical picture. Although microscopic hematuria is usually present, grossly bloody urine is infrequent at this late stage. Without treatment, the prognosis is poor; relentless progression to uremia and death is the rule. The rate of progression is extremely variable.