Causes of acute renal failure can be divided into three categories: 1) prerenal, due to inadequate perfusion; 2) postrenal, due to obstruction of outflow; and 3) intrinsic, due to injury to renal parenchyma. Among the latter, diseases of, or injury to, glomeruli, vessels, interstitium, or tubules may lead to a decrease in glomerular filtration rate (GFR).

Glomerular diseases that lead to acute renal failure are the proliferative glomerulonephritides, including postinfectious and membranoproliferative glomerulonephritis secondary to glomerular deposition of immune complexes. If glomerular injury is severe enough to damage the glomerular basement membrane, leakage of fibrin and other plasma proteins stimulates formation of cellular extracapillary “crescents” composed of epithelial cells and monocytes and macrophages. Crescents may form as a result of an inflammatory reaction to immune complexes formed to nonglomerular antigens; antibody reaction to intrinsic glomerular antigens, as in anti-glomerular basement membrane disease; and, in the absence of immune complexes, the pauci-immune processes, which include the small vessel vasculitides, including Wegener’s granulomatosis and microscopic polyarteritis. Immunohistologic examination and electron microscopy play important roles in the diagnosis of these processes. Extensive crescent formation is accompanied by rapidly progressive acute renal failure. The urine sediment in these diseases often contains red blood cells and red cell casts.

Vascular diseases (involving veins, arteries, or arterioles and capillaries) can lead to hypoperfusion and acute renal failure. Venous thrombosis, most often due to trauma or a nephrotic state, and arterial thrombosis due to trauma or vasculitis, cause parenchymal ischemia and
infarction. Small vessel vasculitides involve small arteries, arterioles, and glomerular capillaries, causing injury and necrosis in the glomerular tuft, which may result in crescent formation. Thrombotic microangiopathies result from endothelial injury damage in small arteries and arterioles, producing thrombosis, obstruction to blood flow, and glomerular hypoperfusion. Urine sediment in these diseases often shows hematuria or cellular casts, reflecting ischemia.

Interstitial inflammatory processes lead to acute renal failure via compression of peritubular capillaries or injury to tubules. Causes of acute interstitial nephritis include infection, and immune-mediated reactions. With infection, polymorphonuclear leukocytes may be seen in tubules as well as in interstitium. Inflammatory infiltrates in hypersensitivity reactions, often due to drug exposure, feature eosinophils. Immunohistologic studies may reveal the presence of immune complexes; immune complex deposition around tubules occurs as a primary process or associated with immune glomerular injury. Tubulitis is seen when the inflammatory reaction extends into the tubular epithelium. Epithelial cell injury is often produced by such inflammatory processes. The urine sediment reveals white blood cells and white cell casts, which may include numerous polymorphonuclear leukocytes or eosinophils.

The most common cause of acute renal failure is injury to tubule epithelium. Primary tubule cell injury typically results from ischemia, toxic injury, or both. Cell injury results in disruption of the epithelium and its normal reabsorptive functions, and may lead to obstruction of tubule lumens. Cell exfoliation often occurs, and intact cells and cell fragments and debris can be seen in the urine sediment; these may be in the form of casts. Necrotic cells may be seen in situ along the tubule epithelium or in the tubule lumen, but often overt cell necrosis is not prominent. Apoptosis of tubule cells is seen after injury as well.

**Glomerular Diseases**

**FIGURE 9-1** (see Color Plate)

Early postinfectious glomerulonephritis. Numerous polymorphonuclear leukocytes in glomerular capillary loops contribute to the hypercellular appearance of the glomerulus. There is also a segmental increase in mesangial cells (hematoxylin and eosin, original magnification × 400). This reactive inflammatory process occurs in response to glomerular deposition of immune complexes, including the large subepithelial “hump-like” deposits which are typical of post-infectious glomerulonephritis. The glomerulonephritis is usually self-limited and reversible, and especially with appropriate treatment of the underlying infection, long-term prognosis is excellent [1].

**FIGURE 9-2** (see Color Plate)

A large epithelial crescent fills Bowman’s space and compresses the capillary loops in the glomerular tuft. This silver stain highlights the glomerular mesangium and the basement membrane of the glomerular capillaries (silver stain, original magnification × 400). The patient presented with hematuria and acute renal failure. Immunostains were negative in this case, a finding consistent with a pauci-immune process. The differential diagnosis includes small vessel vasculitis, and anti-neutrophil cytoplasmic antibody may be positive. Crescentic glomerulonephritis may also occur with anti-glomerular basement membrane antibody disease, or as a complication of immune complex glomerulonephritis [2].
Urine sediment of a patient with acute renal failure revealing red blood cells and some red blood cell casts (original magnification × 600). Biopsy in this case revealed crescentic glomerulonephritis. However, hematuria may be seen in any proliferative glomerulonephritis or with parenchymal infarcts. The “casts” assume the cylindrical shape of the renal tubules, and confirm an intrarenal source of the blood in the urine. Fragmented or dysmorphic red blood cells may be seen when the red cells have traversed through damaged glomerular capillaries.

Vascular Diseases

An early thrombus is seen in a small renal artery in a patient with patchy cortical infarction (original magnification × 250). The patient presented with acute renal failure. The thrombosis may be due to a hypercoagulable state (eg, disseminated intravascular coagulation) or endothelial injury (eg, hemolytic uremic syndrome). If the cortical necrosis is patchy, recovery of adequate renal function may occur [3].

A parenchymal infarct in a patient with renal vein thrombosis (hematoxylin and eosin, original magnification × 200). A few surviving tubules and a rim of inflammatory cells are seen at the periphery of the infarct. Infarcts may also be seen with arterial thromboses, and with severe injury to the microvasculature, as occurs in thrombotic microangiopathies [3]. If the process is extensive, acute cortical necrosis may occur, often leading to irreversible renal failure.
Acute Renal Failure

FIGURE 9-6 (see Color Plate)
A fine-needle aspirate in renal infarction. A, Low magnification shows many degenerating cells with a "dirty background" containing cellular debris and scattered neutrophils. Compare to acute tubular necrosis, which has only scattered degenerated or necrotic cells without the extensive necrosis and cell debris. Neutrophils may be numerous if the edge of an infarct is aspirated (May-Grunwald Giemsa, original magnification × 40). B, Diffusely degenerated and necrotic cells with condensed and disrupted cytoplasm and pyknotic nuclei, and an adjacent neutrophil. No significant numbers of viable tubule epithelial cells remain (May-Grunwald Giemsa, original magnification × 160).

FIGURE 9-7 (see Color Plate)
A small artery with severe inflammation in a patient with a small vessel vasculitis. The wall of the vessel is infiltrated by lymphocytes, plasma cells, and eosinophils (hematoxylin and eosin, original magnification × 250). The patient was p-ANCA positive. ANCA may play a pathogenic role in the vasculitis process [4]. Vasculitis in the kidney is often part of a systemic syndrome, but may occur as an apparently renal-limited process.

FIGURE 9-8 (see Color Plate)
Microangiopathic changes in a small artery, with endothelial activation, evidenced by the large endothelial cells with hyperchromatic nuclei and vacuolization. There is intimal edema with some cell proliferation, and a prominent band of fibrinoid necrosis is seen; the latter appears dark red-pink on this hematoxylin-eosin stain, and represents insudation of fibrin and plasma proteins into the wall of the injured vessel (original magnification × 250). The differential diagnosis includes hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, malignant hypertension, scleroderma, and drug toxicity, the latter due most commonly to mitomycin C or cyclosporine/FK506 [5].
9.5 Renal Histopathology, Urine Cytology, and Cytopathology of Acute Renal Failure

**FIGURE 9-9 (see Color Plate)**
A cast of necrotic tubular cells in urine sediment (Papanicolaou stain, original magnification × 400). The most likely causes of damage to the renal tubules with such findings in the urinary sediment are severe ischemia/infarction, or tubular necrosis due to exposure to toxins which injure the renal tubules. The latter include antibiotics, including aminoglycosides and cephalosporins, and chemotherapeutic agents.

**FIGURE 9-10 (see Color Plate)**
Interstitial nephritis with edema and a mononuclear inflammatory infiltrate. Eosinophils in the infiltrate suggest a possible hypersensitivity reaction (hematoxylin and eosin, original magnification ×400). Drugs are the most common cause of such a reaction, which often presents with acute renal failure [6]. Inflammatory cells and cell casts may be seen in the urine sediment in these cases, as inflammatory cells infiltrate the tubular epithelium.

**FIGURE 9-11 (see Color Plate)**
Tubulitis, with infiltration of mononuclear cells into the tubular epithelium (hematoxylin and eosin, original magnification ×400). There is a mononuclear infiltrate and edema in the surrounding interstitium. Tubule cells may show evidence of lethal or sublethal injury as the inflammatory cells release damaging enzymes. Tubulitis is often seen in interstitial nephritis especially if the targets of the inflammatory reaction are tubular cell antigens or antigens deposited around the tubules. Immunofluorescence may reveal granular or linear deposits of immunoglobulin and complement around the tubules.
Acute Renal Failure

**FIGURE 9-12** (see Color Plate)
Polymorphonuclear leukocytes forming a cast in a cortical tubule (hematoxylin and eosin, original magnification × 400). Note edema and inflammation in adjacent interstitium. These intratubular cells are highly suggestive of acute infection, and may be seen in distal as well as proximal nephron as part of an ascending infection. Intratubular PM L may also be seen in vasculitis and other necrotizing glomerular processes, in which these cells escape across damaged areas of the inflamed glomerular tuft.

**FIGURE 9-13** (see Color Plate)
Fine-needle aspirate of acute infectious interstitial nephritis (acute pyelonephritis). A 25-gauge needle attached to a 10-cc syringe was utilized to withdraw the aspirate into 4 cc of RPMI-based medium. The specimen was then cytocentrifuged and stained with May-Grunwald Giemsa. A, The renal aspirate contains large numbers of intrarenal neutrophils, which are focally undergoing degenerative changes with cytoplasmic vacuolization and nuclear breakdown. In bacterial infection there are many infiltrating neutrophils and there may be associated necrosis of tubule epithelial cells (original magnification × 80). B, A neutrophil contains phagocytosed bacteria within the cytoplasm; bacteria stain with Giemsa, so are readily detectable in this setting. Adjacent tubule epithelial cells have cytoplasmic granules but do not phagocytize bacteria (original magnification × 160).

**FIGURE 9-14** (see Color Plate)
Numerous polymorphonuclear leukocytes (PM L) in the urine sediment of a patient with acute pyelonephritis (hematoxylin and eosin, original magnification × 400). Some red blood cells and tubular cells are seen in the background of this cytocentrin preparation. PM L may be found in the urine with acute infection of the lower urinary tract as well, or as a contaminant from vaginal secretions in females. PM L casts, on the other hand, are evidence that the cells are from the kidney.
Renal Histopathology, Urine Cytology, and Cytopathology of Acute Renal Failure

**FIGURE 9-15** (see Color Plate)
Fine-needle aspirate from patient with intrarenal cytomegalovirus (CMV) infection. A. There are activated and transformed lymphocytes with immature nuclear chromatin and abundant blue cytoplasm that infiltrate the kidney in response to the infection; large granular lymphocytes (NK cells) may be seen as well, but few neutrophils. Similar activated lymphocytes, NK cells, and atypical monocytes can be observed within the peripheral blood. The tubule epithelial cells are virtually never seen to contain CMV inclusions in aspirate material, in contrast to core biopsy specimens. All intrarenal viral infections have a similar appearance, and immunostaining or in situ hybridization is required to identify specific viruses (May-Grunwald Giemsa, original magnification × 80). B. Tubular epithelial cells stained with antibody to CMV immediate and early nuclear proteins in active intrarenal CMV infection. With an immunoalkaline phosphatase method, cytoplasmic and prominent nuclear staining for these early proteins are observed in the tubular epithelium. In very early infection, neutrophils also may have cytoplasmic staining for these proteins (original magnification × 240).

**FIGURE 9-16** (see Color Plate)
Numerous eosinophils in an interstitial inflammatory infiltrate. Eosinophils may be diffuse within the infiltrate, but may also be clustered, forming “eosinophilic abscesses,” as in this area (hematoxylin and eosin, original magnification × 400). Eosinophils may also be demonstrated in the urine sediment. Drugs most commonly producing acute interstitial nephritis as part of a hypersensitivity reaction include: penicillins, sulfonamides, and nonsteroidal anti-inflammatory drugs [6]. The patient had recently undergone a course of therapy with methicillin. The interstitial nephritis may be part of a systemic reaction which includes fever, rash, and eosinophilia.
Acute Renal Failure

FIGURE 9-17 (see Color Plate)
Fine-needle aspirate of acute allergic interstitial nephritis. A, The aspirate contains numerous lymphocytes, occasional activated lymphocytes, and eosinophils without fully transformed lymphocytes, corresponding to the inflammatory component within the tubulointerstitium observed on routine renal biopsy. Monocytes often are present (May-Grunwald Giemsa, original magnification × 80). B, Higher magnification showing the typical infiltrating cells, including a monocyte, activated lymphocyte, and an eosinophil. A neutrophil is present, likely owing to blood contamination (May-Grunwald Giemsa, original magnification × 160).

Tubular Diseases

FIGURE 9-18 (see Color Plate)
Severe vacuolization of tubular cells in injured tubular epithelium (hematoxylin and eosin, original magnification × 400). The vacuoles reflect cell injury and derangement of homeostatic mechanisms that maintain the normal intracellular milieu. In this case, the vacuoles developed on exposure to intravenous immunoglobulin in a sucrose vehicle; the morphology is reminiscent of the severe changes produced by osmotic agents. While generally a nonspecific marker of cell injury, a distinctive pattern of “isometric” vacuolization, in which there are numerous intracellular vacuoles of uniform size (not shown here) is very typical of cyclosporine/FK506 effect [6].

FIGURE 9-19 (see Color Plate)
Necrotic tubular cells and cell debris in tubular lumina. One tubule shows extensive cell loss, with tubular epithelium lined only by a very flattened layer of cytoplasm. The dilated lumen contains numerous necrotic tubular cells with pyknotic nuclei. Several tubules contain cell debris and one contains red blood cells (hematoxylin and eosin, original magnification × 250). Such changes are more often seen with toxic than with ischemic injury [6], unless the latter is very severe.
This micrograph shows sites of cell exfoliation, attenuation of remaining cells, and reactive and regenerative changes (hematoxylin and eosin, original magnification × 400). Exfoliation occurs with disruption of cell-cell and cell-substrate adhesion, and may involve viable as well as non-viable cells [7]. Reactive and regenerative changes may include basophilia of cell cytoplasm, increased nuclear:cytoplasmic ratio, heterogeneity of nuclear size and appearance, hyperchromatic nuclei and mitotic figures.

Outer medulla shows in situ necrosis and loss in medullary thick ascending limb (hematoxylin and eosin, original magnification × 250). Tubules contain cells and cell debris. Changes reflect ischemic injury. Impaction of cells and cast material may lead to tubular obstruction, especially in narrow regions of the nephron. Adhesion molecules on the surface of exfoliated cells may contribute to aggregation of cells within the tubule and adhesion of detached cells to in situ tubular cells [8].

Fine-needle aspirate showing acute tubular cell injury and necrosis. A. The aspirate shows scattered tubular epithelial cells with swelling and focal degenerative changes, and a minimal associated inflammatory infiltrate. There is no significant background cell debris (May-Grunwald Giemsa, original magnification × 40). B. One tubular cell is degenerated with reduction in cell size, condensed gray-blue cytoplasm, and a pyknotic nucleus. Another cell has more advanced necrosis with additional cytoplasmic disruption and a very small pyknotic nucleus. Compare the adjacent swollen damaged tubular cell which has not yet undergone necrosis (May-Grunwald Giemsa, original magnification × 160).
Acute Renal Failure

**FIGURE 9-23 (see Color Plate)**
Urine sediment from a patient with acute tubular injury showing tubular cells and cell casts (Papanicolaou stain, original magnification × 250). Many of these cells are morphologically intact, even by electron microscopy. Studies have shown that a significant percentage of the cells shed into the urine may exclude vital dyes, and may even grow when placed in culture, indicating that they remain viable. Such cells clearly detached from tubular basement membrane as a manifestation of sub-lethal injury [7].

**FIGURE 9-24 (see Color Plate)**
Myoglobin casts in the tubules of a patient who abused cocaine. A, Hematoxylin and eosin stained casts have a dark red, coarsely granular appearance (original magnification × 250). B, Immunoperoxidase stain for myoglobin confirms positive staining in the casts (original magnification × 250). These casts may obstruct the nephron, especially with dehydration and low tubular fluid flow rates. Rhabdomyolysis with formation of intrarenal myoglobin casts may also occur with severe trauma, crush injury, or extreme exercise.
FIGURE 9-25 (see Color Plate)
Apoptosis of tubular cells following tubular cell injury. Note the shrunken cells with condensed nuclei and cytoplasm in the central tubule. The patient had presumed ischemic injury (hematoxylin and eosin, original magnification × 400). The role of apoptosis in injury to the renal tubule remains to be defined. The process may be difficult to quantitate, since apoptotic cells may rapidly disintegrate. In experimental models, the degree of apoptosis versus coagulative necrosis occurring following injury is related to the severity and duration of injury, with milder injury showing more apoptosis [9].

FIGURE 9-26
Apoptosis-schematic of histologic changes in tubular epithelium. The process begins with condensation of the cytoplasm and of the nucleus, a process which involves endonucleases, which digest the DNA into ladder-like fragments characteristic of this process. The cell disintegrates into discrete membrane-bound fragments, so-called "apoptotic bodies." These fragments may be rapidly extruded into the tubular lumen or phagocytosed by neighboring epithelial cells or inflammatory cells. (Modified from Arends, et al. [10]; with permission.)
FIGURE 9-27
A schematic showing the relationship between morphologic and functional changes with injury to the renal tubule due to ischemia or nephrotoxins. Morphologic changes are shown in italics.

References


