depletion, advanced age, and exposure to other nephrotoxins. The incidence of AKI may be 25% and approaches 50% in patients with underlying risk factors. ATN occurs from both ischemic tubular injury (prolonged decrease in renal blood flow) and direct toxicity (osmotic cellular injury, oxidative stress, inflammation). Large radiocontrast volumes increase risk, whereas low-osmolar and iso-osmolar radiocontrast agents are less nephrotoxic than high-osmolar material.

The antiviral agents cidofovir and tenofovir, once they have entered the cell from the peritubular blood via the human organic anion transporter 1 on the basolateral membrane, cause AKI through disruption of mitochondrial and other cellular functions. Several chemotherapeutic agents, including the platinum-based drugs, ifosfamide, mithramycin, imatinib, pentostatin, and pemetrexed, cause ATN through direct toxic effects. As with other nephrotoxins, part of their ability to induce ATN resides in the renal handling by the kidneys (transport through tubular cells) as they are being excreted. In addition, zoledronate, the polymixins, high-dose vancomycin, foscarnet, and deferasirox also cause nephrotoxic ATN. AKI prevention is best achieved by judicious prescription of these drugs to high-risk patients, appropriate dose adjustments, avoidance of superimposed volume depletion, and close monitoring with early markers of injury such as urine microscopy.

Pigment Nephropathy

Pigment nephropathy represents the nephrotoxic renal tubular effects of endogenously produced substances. The most common examples are overproduction of heme moieties in serum that are eventually filtered at the glomerulus and excreted in urine. With severe rhabdomyolysis, the heme pigment released from muscle is myoglobin. AKI develops in the setting of myoglobinuria from the combination of direct myoglobin tubular toxicity (in an acid urine), volume depletion, and obstructing myoglobin casts. Therapy includes intravenous fluids (the addition of bicarbonate is questionable), supportive care, and sometimes RRT. Most patients recover kidney function to near-baseline.

Massive intravascular hemolysis from various causes (e.g., immune-mediated, microangiopathic) is associated with hemoglobinuria, which induces tubular injury by promoting the formation of reactive oxygen species and by reducing renal perfusion through inhibition of nitric oxide synthesis. Therapy is directed at the primary cause, with intravenous fluids and supportive care. Most patients ultimately recover kidney function.

Crystal Nephropathy

AKI may result from crystal deposition in distal tubular lumens after massive rises in uric acid or therapy with certain medications. Risk factors for AKI due to crystal deposition are underlying kidney disease and intravascular volume depletion. Acute uric acid nephropathy from urate crystal deposition and tubular obstruction develops in patients with massive tumor lysis syndrome.

Drugs such as sulfadiazine promote intratubular deposition of sulfa crystals in acid urine, whereas acyclovir crystal deposition occurs after large, rapid intravenous doses of the drug, and atazanavir and indinavir crystal deposition occurs in the setting of volume contraction and urine pH higher than 5.5. Ciprofloxacin can cause AKI due to intratubular crystal deposition when administered in excessive doses, primarily in patients with unrecognized kidney disease and those with alkaline urine. In addition, methotrexate or large doses of intravenous vitamin C (producing oxalate) can cause AKI due to intratubular crystal deposition.

Weight loss therapies such as bariatric surgery with small bowel bypass and orlistat, through induction of malabsorption, cause enteric hyperoxaluria and calcium oxalate crystal deposition, an entity known as acute oxalate nephropathy (E-Fig. 31-5). Sodium phosphate–containing bowel purgatives have also been associated with AKI due to acute phosphate nephropathy, an entity characterized by calcium phosphate intratubular crystal deposition.

Diagnosis of crystal nephropathy is based on a history of exposure to a culprit agent or an underlying disease state associated with excessive crystal production.

Osmotic Nephropathy

Osmotic nephropathy is a little known entity that can promote AKI through the induction of proximal tubular swelling, cell injury, and occlusion of intratubular lumens. The hyperosmolar and unmetabolizable nature of substances such as sucrose, dextran, mannitol, the sucrose excipient of intravenous immune globulin, and hydroxyethylstarch underlies the pathophysiology of this kidney lesion. Cells develop severe swelling with cytoplasmic vacuoles, disturbing cellular integrity and occluding tubular lumens. AKI results from this abnormal tubular process when patients with underlying kidney disease or other risk factors for kidney injury (e.g., intravascular volume depletion, older age) receive these hyperosmolar substances. AKI is dose related and may require RRT. Although most patients recover from AKI, CKD can result. Therapy is primarily supportive, along with avoidance of further exposure to these agents.

Interstitial Disease

Interstitial disease develops in the setting of infection with certain agents, systemic diseases, infiltrative malignancies, and exposure to some medications. Of these, drug-induced disease is by far the most common entity, especially in the hospitalized patient. The syndrome of AIN is characterized by AKI and a variety of clinical findings. The clinical presentation varies based on the offending agent and the host response. As an example, β-lactam antibiotics frequently cause the classic triad of fever, maculopapular skin rash, and eosinophilia. Arthralgias, myalgias, and flank pain may also occur. Aside from causing AKI, NSAIDs can rarely lead to allergic or extrarenal manifestations such as fever, rash, or eosinophilia.

Urinalysis may reveal dipstick-positive (trace to 1+) protein, blood, and leukocyte esterase. Urine microscopy may be bland (~20%), but more often, the urine sediment demonstrates white blood cells (WBCs), RBCs, WBC casts, and granular casts. Wright or Hansel stain may reveal eosinophils in the urine, but neither of these tests is sensitive or specific for AIN.

The diagnosis is best confirmed by kidney biopsy. A cellular infiltrate consisting of lymphocytes, monocytes, eosinophils, and plasma cells is typically present; interstitial edema and fibrosis vary based on the time of drug exposure (E-Fig. 31-6). Tubulitis, or invasion of lymphocytes into the tubular cells, is frequently