CHAPTER

36 Acute Kidney Injury Associated with Pigmenturia or Crystal Deposits

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ACUTE KIDNEY INJURY RESULTING FROM HEME PIGMENTS

Myoglobinuric Acute Kidney Injury

Rhabdomyolysis is a potentially life-threatening syndrome involving damage and the breakdown of skeletal muscle causing myoglobin and other intracellular proteins and electrolytes to be released into the circulation. This syndrome is a relatively common cause of acute kidney injury (AKI)* and accounts for 7% to 10% of AKI in the United States.[1] Perhaps the first historical suggestion of rhabdomyolysis goes back to biblical times where it is related that the Israelites became ill and died after eating large quantities of quail, which had probably fed on hemlock seeds. In modern times, the initial description of the consequences of traumatic muscle injury on kidney function is attributed to Bywaters and Beall,[2] who vividly documented the brown-black granular casts, a reduction in urinary output, hyperkalemia, and ultimately, death in the victims of crush injuries at the time of the London bombing during World War II. In addition, Bywaters et al.[3,4] were the first to establish a definite pathophysiologic relationship between crush injury, myoglobinuria, and acute tubular necrosis.

Causes of Rhabdomyolysis and Myoglobinuria

A variety of conditions and diseases can lead to rhabdomyolysis and AKI, and the list of causes is constantly being expanded with new case reports (Table 36.1). Although the list is long, it can be divided into eight basic categories: (1) direct muscle injury, (2) drugs and toxins, (3) genetic disorders, (4) infections, (5) excessive muscular activity, (6) ischemia, (7) electrolyte and endocrine/metabolic disturbances, and (8) immunologic diseases. The common denominator for all the causes is a disruption of normal skeletal muscle cell structure or metabolism leading to derangements in Ca^{2+} homeostasis. Adenosine triphosphate (ATP) depletion further interferes with Ca^{2+} sequestration, leading to lethal intracellular Ca^{2+} overload that activates a number of autolytic enzymes, causing myofibril and membrane damage.[5] The subsequent death and lysis of skeletal muscle cells results in the release of intracellular contents into the circulation. In the United States, the three most common causes of rhabdomyolysis are drug abuse (with a substantial percentage related to ethanol use), muscle compression, and seizures.[1]

Crush injuries[1,6,7] and prolonged compression of the limbs can lead to massive rhabdomyolysis and its sequelae, including AKI. Significant volume and electrolyte imbalance may ensue due to a massive influx of extracellular fluid and solutes into and efflux of major intracellular ions such as potassium and phosphate out of the damaged cells.[1,7]

Drugs and toxins have also been implicated in causing rhabdomyolysis.[8,9] Several mechanisms underlie drug- and toxin-induced rhabdomyolysis, including (1) drug-induced coma leading to compression of a limb; (2) excessive muscular activity (e.g., phencyclidine, LSD, hemlock); (3) drug-induced hyperthermia; (4) drug-induced vasoconstriction with muscle ischemia (e.g., cocaine); (5) impaired ATP formation (e.g., cyanide, salicylates); (6) the induction of potassium or phosphorus depletion (e.g., diuretics); (7) a hypersensitivity reaction resulting in myositis; (8) a direct toxic effect on skeletal muscle cells (e.g., ethanol); and (9) drugs whose mechanism of toxicity is still controversial (e.g., statins).[10,11] Although certain drugs, such as heroin[12] or ethanol,[13] may have a direct toxic effect on skeletal muscle cells, a more important factor in causing rhabdomyolysis is the occurrence of a coma after their use leading to muscle compression and ischemia. In addition, drug use may be associated with other conditions that predispose one to rhabdomyolysis. For example, in the alcoholic patient, concomitant hypokalemia,[14] hypophosphatemia,[15] and starvation[16] may contribute to rhabdomyolysis. The presence of multiple etiologic factors may be a common scenario, as noted in a large clinical series by Gabow et al.,[17] in which more than

*In recent years, the term acute kidney injury (AKI) has replaced acute renal failure (ARF), because AKI denotes the entire clinical spectrum from mild increases in serum creatinine to overt renal failure (Molitoris et al. J Am Soc Nephrol. 2007;18:1992–1994).

36.1 Causes of Rhabdomyolysis

- Traumatic muscle injury
  - Crush injuries
  - Compression/pressure necrosis
  - Severe burns
  - Contact sports
  - Direct muscle trauma
- Drugs and toxins (partial list)
  - Ethanol
  - Heroin
  - Barbiturates
  - Cocaine
  - Amphetamines
  - Benzodiazepines
  - Phencyclidine
  - HMG-CoA reductase inhibitors (statins)
  - Fibric acid derivatives (clofibrate, gemfibrozil)
  - Hemlock
  - Salicylates
  - Carbon monoxide
  - Ethylene glycol
  - Isopropyl alcohol
  - Snake and insect venoms
  - Succinylcholine
  - Colchicine
  - Propofol
  - Paraphenylenediamine
  - Colchicum autumnale (autumn crocus)
  - Monensin
- Genetic disorders
  - Phosphorylase deficiency (McArdle disease)
  - Phosphofructokinase deficiency
  - α-Glucosidase deficiency
  - Carnitine palmityltransferase deficiency
  - Amylo-1,6-glucosidase deficiency
  - Phosphohexoseisomerase deficiency
- Infections (partial list)
  - Influenza
  - Tetanus
  - Gas gangrene
  - Legionnaires' disease
  - Shigellosis and salmonellosis
  - Coxsackievirus
  - Leptospirosis
  - Streptococcus
  - HIV
- Excessive muscular activity
  - Vigorous exercise
  - Seizures/status epilepticus
  - Delirium tremens
  - Status asthmaticus
  - Psychotic muscle contractions
  - Tetany
- Ischemia
  - Arterial occlusion
  - Compression
- Electrolyte and endocrine/metabolic disorders
  - Hypokalemia
  - Hypophosphatemia
  - Hypothyroidism
  - Diabetic ketoacidosis
  - Diabetic hyperosmolar nonketotic coma
  - Hypothermia and hyperthermia
- Immunologic disease
  - Polymyositis
  - Dermatomyositis

HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A.

one factor capable of injuring muscles was present in 51 of 87 episodes of rhabdomyolysis. One such etiologic factor demonstrating the variable causes of rhabdomyolysis is fire ant bites. In a recent case report, a patient was described who developed AKI because of rhabdomyolysis after extensive red fire ant bites.[18] It was suggested that formic acid, an important constituent of fire ant venom, was the underlying mechanism for rhabdomyolysis. In small doses, formic acid is an antibiotic, but in larger doses it acts as an inhibitor of the mitochondrial cytochrome oxidase complex causing tissue suffocation and, consequently, cell death.[18]

Various hereditary enzyme deficiencies and defects have been associated with rhabdomyolysis and myoglobinuria. These are divided into groups of patients with hereditary deficiency of enzyme(s) in (1) glycolytic/glycogenolytic pathways; (2) the fatty acid oxidation pathway; (3) the Krebs cycle; (4) the pentose phosphate pathway; (5) the purine nucleotide cycle; (6) the mitochondrial respiratory chain; (7) patients prone to malignant hyperthermia; and (8) other miscellaneous causes such as sarcoplasmic Ca^{2+}-ATPase deficiency.[19]

The myositis occasionally associated with infectious diseases such as influenza, HIV, and leptospirosis can lead to a

disruption of skeletal muscle cells and thus rhabdomyolysis and myoglobinuria.[19,20] In addition, infections like gas gangrene produce a clostridial toxin that is directly myotoxic.[20]

Excessive muscular activity has been increasingly recognized as a common and preventable cause of rhabdomyolysis.[21,22] Strenuous and exhaustive exercise, especially in deconditioned men (so-called "white collar" rhabdomyolysis), can result in serious rhabdomyolysis.[23] Contributing factors to this syndrome include exercising in a hot or humid environment, volume depletion, fasting, eccentric muscle contractions (e.g., running downhill), preexistent muscle injury (e.g., alcoholic myopathy), and male sex.[23] Intense muscle contractions deplete energy reserves, thus disrupting normal cellular transport processes and permitting calcium to accumulate in the cell, resulting in the activation of proteolytic enzymes and cell death. Based on a number of studies,[23] physical training raises the threshold and induces a degree of resistance to the development of exertional rhabdomyolysis. Training may induce this adaptation by increasing the number of collateral blood vessels, hence improving oxygen delivery, fuel storage, and use. Other conditions associated with excessive muscle contractions and significant rhabdomyolysis include seizures, tetanus, delirium tremens, electrical shock injury, and extensive burns.

Severe potassium deficiency can lead to rhabdomyolysis, myoglobinuria, and AKI. Hypophosphatemia, especially in the setting of severe alcoholism, has been associated with muscle cell injury and rhabdomyolysis.[15] Other metabolic conditions that have been reported to cause rhabdomyolysis include hyperaldosteronism, ketoacidosis, hypothyroidism, and deranged core body temperature.[19]

Myoglobin Metabolism

Myoglobin is composed of a folded polypeptide portion (globin) and a prosthetic group, heme, which contains an atom of iron.[24,25] Based on tracer studies, the half-life of myoglobin in the circulation varies from 1 to 3 hours; after 6 hours, it disappears completely.[24,25] Small quantities of myoglobin (milligram amounts) released during normal conditions are probably cleared by the reticuloendothelial system. Because of its relatively small molecular weight and size, larger quantities of myoglobin released from the muscle in states of injury or disease are readily filtered at the glomerulus and thus can be cleared by renal mechanisms.

In human circulation, myoglobin appears to be bound to an α_2-globulin that has a binding capacity of 23 mg per deciliter. Because myoglobin is loosely bound to α_2-globulin at concentrations below 23 mg per deciliter, approximately 15% to 50% of the myoglobin is in an unbound state and is filtered (fractional clearance relative to inulin, 0.75) and excreted in the urine. This interesting kinetic relationship between myoglobin and its binding protein probably explains why myoglobin is detected in the urine when plasma levels are less than 23 mg per deciliter.[24,25] According to Kagen,[26] the effective renal threshold for myoglobin occurs when the plasma concentration exceeds 0.5 to 1.5 mg per deciliter. Based on a distribution volume of myoglobin of 28.5 L and a muscle myoglobin content of 4 mg per gram, Knochel[27] has calculated that injury of approximately 102 g of muscle would be required to exceed a renal threshold of 1.5 mg per deciliter. Beyond this threshold, the factors that determine the urinary concentration and the excretion rate of myoglobin include (1) the plasma concentration of myoglobin, (2) the extent of myoglobin binding in plasma, (3) glomerular filtration rate (GFR), and (4) urine flow rate.

Myoglobin is visible in plasma or urine to the unaided eye when the concentration exceeds 100 mg per deciliter. Because of the relatively rapid renal clearance of myoglobin, visible plasma levels of myoglobin have never been reported. Knochel[27] has estimated that a visible plasma level of myoglobin would require the destruction of 7.1 kg of muscle in an anephric patient. In contrast, because myoglobin is cleared rapidly in patients with a normal renal function, visible myoglobinuria is achieved with far less muscle necrosis. For example, necrosis of only 178 g of muscle, achieving a plasma myoglobin level of only 2.5 mg per deciliter, is sufficient to produce visible myoglobinuria in a patient with normal renal function excreting concentrated urine.[27] However, reduced renal function or a high urine flow rate decreases the concentration of myoglobin in urine, thus diminishing the use of a visual inspection of the urine to detect myoglobinuria for a given amount of muscle necrosis. In these situations, benzidine, guaiac, or orthotoluidine (dipstick) tests detect levels as low as 0.5 mg per 100 mL. These tests, however, do not distinguish between myoglobin and hemoglobin. This can be accomplished by immunodiffusion.[28] Multiple alternative methods of detection are now available, including hemagglutination inhibition, radioimmunoassay, and complement fixation.[19]

Given the rapid renal clearance of myoglobin (1 to 6 hours), its presence in the blood or urine may not be the most sensitive method to detect rhabdomyolysis. In contrast, creatine kinase, an intracellular muscle enzyme, appears to be a more sensitive plasma marker for rhabdomyolysis because of its slower clearance (serum half-life, 1.5 days), and therefore is the preferred diagnostic modality.[29]

Pathophysiology of Myoglobinuric and Hemoglobinuric Acute Kidney Injury

Given the biochemical similarity between myoglobin and hemoglobin, the general consensus that they share a common pathogenetic pathway, and the fact that the classical animal models used to study pigment-induced oliguric AKI share intravascular hemolysis (hemoglobinuria) and rhabdomyolysis (myoglobinuria), the pathogenesis of these two pigments are presented together in this discussion.

The proposed mechanisms by which myoglobinuria or hemoglobinuria cause AKI include (1) hypovolemia and renal ischemia, (2) direct tubular toxicity of myoglobin/hemoglobin, (3) tubular obstruction from heme pigment casts, and (4) glomerular fibrin deposition. As in many clinical syndromes, it is probably the interplay of these proposed

FIGURE 36.1 The pathophysiologic processes involved in myoglobinuric and hemoglobinuric acute kidney injury. (Modified from Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int*. 1996;49:317, with permission.)

mechanisms that results in AKI rather than any one single factor. These interactions are schematized in Figure 36.1.

Hypovolemia and Renal Ischemia

During the initial phase of glycerol-induced AKI (an animal model for rhabdomyolysis), there is a marked reduction in cardiac output (36%), renal blood flow (RBF) (20%), and an increase in renal vascular resistance.[30] Subcutaneous or intramuscular (but not intravenous) glycerol not only produces muscle injury but also causes sequestration of fluid into the injection site.[31] Thus, the hemodynamic changes are due, in part, to the migration of plasma water into the site of injury with consequent severe intravascular volume contraction occurring in this model of myohemoglobinuric AKI. Comparable hemodynamic changes occur in clinical settings that damage and cause necrosis of the skeletal muscle such as crush syndrome.[7] Moreover, the conditions that predispose one to rhabdomyolysis, such as drug-induced coma with accompanying poor oral intake, or excessive insensible fluid losses from exhaustive exercise or burns, contribute to intravascular volume depletion and compromise of renal function.

In the initial phases of glycerol-induced AKI, the reduction in RBF is associated with a redistribution of regional blood flow from the outer to the inner cortex[32] and vasoconstriction of the afferent and efferent arteriole. The proposed mediators of this initial renal vasoconstriction include (1) increased sympathetic nerve activity, (2) augmented activity of the renin–angiotensin system, (3) reduced nitric oxide production and availability, (4) suppressed renal prostaglandin production, (5) increased plasma vasopressin concentration, and (6) glomerular microthrombi.[33] The reduction in nitric oxide may be due to the fact that heme proteins can scavenge this important endogenous vasodilator. Nitric oxide synthase inhibition worsens and nitric oxide supplementation protects against glycerol-induced AKI. This lends support to the protective effects of nitric oxide in the pathogenesis of myoglobin-induced AKI.[34]

The critical role that intravascular volume depletion plays in the pathogenesis of myohemoglobinuric AKI is demonstrated by studies in which volume status is manipulated in the glycerol-treated rat. In initial studies, Oken et al.[35,36] noted that renal damage was ameliorated if the rats ingested adequate quantities of water before the administration of glycerol. Similarly, Hsu et al.[30] found that the reduction in RBF and function in response to the administration of glycerol was attenuated in rats chronically drinking saline compared with rats drinking water. Reineck et al.[37] provided a better understanding of the important temporal relationship

between volume expansion and improvement of renal function in the glycerol-treated rat. Like other investigators, they noted a significant reduction in RBF and GFR after the administration of glycerol. These variables could be restored to normal levels by volume expansion with Ringer's solution at 3 and 6 hours, but not at 18 hours after the administration of glycerol. They concluded that the initial decrease in GFR and the low fractional excretion of sodium was due to a decrease in RBF (renal hypoperfusion), whereas other events (e.g., tubular necrosis) accounted for decreased GFR at later time points. These preclinical studies support the clinical observation that, initially, patients with myoglobinuric AKI have features of prerenal azotemia, including a low urinary fractional excretion of sodium.[38] In addition, they provide the rationale for early use of volume expansion in patients with rhabdomyolysis and hemoglobinuria.

Myoglobin and Hemoglobin Nephrotoxicity. Bywaters and coworkers[2,3] expanded on their original description of the clinical syndrome of rhabdomyolysis-induced AKI to examine the role of myoglobin as a direct nephrotoxin. They noted that rabbits ingesting an acid diet with a urine pH below 6.0 had AKI after the infusion of human myoglobin, whereas rabbits ingesting a normal diet were spared from renal injury.[3] Other investigators[39,40] have confirmed this observation that intravenous infusions of myoglobin are relatively benign but can become highly nephrotoxic in the setting of acidemia/aciduria and volume depletion. Vetterlein et al.[41] demonstrated that infusions of myoglobin had no effect on RBF in normal rats, but worsened RBF in hypotensive animals. Thus, it appears that heme proteins can intensify the degree of vasoconstriction in the setting of hypovolemia. This may explain the clinical observation that the mere presence of myoglobinuria or a markedly elevated creatine kinase at the time of hospital admission had little predictive value in determining who experiences AKI.[17] These observations suggest that other conditions (i.e., volume depletion, acidemia) are required for renal injury to occur.

To address the question of why heme pigments are nephrotoxic only in certain metabolic conditions, Braun et al.[31] investigated the effect of breakdown products of heme pigments on renal tubular transport. First, they noted that 4 hours after a subcutaneous glycerol administration to rats there was both swelling and pallor of the proximal tubule and depression of normal tubular uptake of hippurate and tetraethylammonium. The investigators measured the uptake of hippurate in renal cortical slices incubated with various specific heme proteins or their derivatives and found that incubation with hemoglobin did not depress uptake if the pH of the medium was kept at 7.4. However, uptake was depressed when the pH was lowered to 5.4 or during hypoxic conditions. In an acidic medium (pH $<$5.6), both myoglobin and hemoglobin dissociate into ferrihemate (hematin; molecular weight, 670 Da) and their respective globin moieties.[42] Incubation with ferrihemate, regardless of the pH of the medium, depressed the uptake of hippurate in the renal cortical slices, whereas incubation with either globin or albumin alone had no significant effect on transport. The inhibitory action of ferrihemate on hippurate transport could be mitigated if the incubation medium also contained albumin, which presumably bound the ferrihemate. Intravenous injection of ferrihemate has been shown to cause glomerular and tubular damage in the dog.[43] Therefore, it has been proposed that after filtration by the glomerulus, myoglobin or hemoglobin is converted to ferrihemate in the presence of an acid tubular fluid, or after exposure to the acid pH of cellular lysosomes, and it is this metabolite that is directly nephrotoxic.

These and other studies implicate the heme moiety as a potent pro-oxidant molecule.[44,45] It is well established that free heme can facilitate the production of reactive oxygen species via Fenton/Haber-Weiss reactions. Under physiologic conditions, free heme is sequestered by heme binding proteins, and oxidative stress can cause the release of heme, thereby increasing free heme levels. In addition, evidence suggests that the iron component of heme is the culprit of heme-induced oxidative damage.[44,45] The central role of iron has been substantiated by a number of studies demonstrating amelioration of both myoglobinuric and hemoglobinuric AKI and lipid peroxidation by the iron chelator, deferoxamine.[46] On the other hand, Zager[47] has also shown that deferoxamine attenuates renal damage in the glycerol-induced model of AKI, but concluded that iron toxicity is mediated by factors other than free radical generation. For example, it has been suggested that heme protein endocytosis in the proximal tubule sensitizes the tubular cell membranes to the damaging effects of phospholipase A_2.[48] In addition, heme proteins appear to deplete cellular ATP stores and, thus, have an adverse effect on cellular energetics.[5] Iron toxicity may be due to redox cycling of the heme moiety from ferrous to ferric and to ferryl oxidation states.[49]

In order to contend with the pro-oxidant heme moiety, the kidney induces antioxidant defensive machinery, including heme oxygenase-1 (HO-1).[44,45] HO-1 catalyzes the rate-limiting step in the oxidative degradation of heme liberating equimolar amounts of iron, carbon monoxide, and biliverdin. Iron in turn induces the expression of ferritin. HO-1 is known to have important antioxidant, anti-inflammatory, and antiapoptotic functions that have been attributed to one or more of its byproducts.[44,45] Nath et al.[50] have demonstrated that the renal induction of both HO-1 and ferritin is increased in the glycerol-induced model of myohemoglobinuric AKI. Prior induction of HO-1 coupled with increased ferritin synthesis attenuated renal damage, whereas pharmacologic inhibition of the enzyme or its gene deletion worsened renal function.[50,51] This increased activity of HO-1, or possibly a broad-based proximal tubular cytoresistance in the kidney, may explain the experimental observation that after induction of myohemoglobinuric AKI rechallenging the animals with a second dose of glycerol does not result in AKI.[52] One speculation is that in the setting of clinical myoglobin-induced AKI, there may be factors contributing to the inhibition of HO-1 and ferritin synthesis, or a

diminution in proximal tubular resistance, resulting in both an accumulation of nephrotoxic iron and in tubular necrosis.

Tubular Obstruction. Filling of the tubular lumen by pigmented casts that become inspissated and obstruct urinary flow with subsequent injury to tubular epithelium is one of the earliest mechanisms proposed to explain the nephrotoxicity of the heme pigments.[53] In their original clinical description of rhabdomyolysis-induced AKI, Bywaters and Beall[2] described the prominent histologic features, including the appearance of tubular obstruction by cellular debris and pigmented casts. It has been suggested that hypovolemia and academia, and the concomitant acidic concentrated urine, facilitate the precipitation of filtered myoglobin or hemoglobin leading to obstructive cast formation.[54] The presence of the Tamm-Horsfall protein in the tubular lumen is critical for heme protein cast formation in the distal nephron. Moreover, an obstructing cast induces urinary stasis, providing for an extended time for proximal tubular heme reabsorption and its attendant tubular toxicity, as noted previously.[55]

Tubular obstruction can decrease GFR either by increasing the tubular pressure and thus decreasing the glomerular transcapillary hydraulic pressure, or by inducing the release of factors (e.g., thromboxane) that cause renal vasoconstriction, thereby reducing glomerular blood flow. The importance of tubular obstruction as a possible mechanism of heme pigment–induced AKI is suggested by the studies of Zager[47] that explored the reasons why mannitol exerts a protective effect against this syndrome. The major beneficial effect of mannitol was attributed to its diuretic effect, which presumably decreased cast formation and proximal tubular uptake of heme proteins. Similarly, alkalinization of the urine may mitigate against myoglobinuric AKI by increasing the solubility of myoglobin (reduced cast formation) and inducing a solute diuresis.[54]

Although there is evidence that tubular obstruction may be a factor in the pathogenesis of the AKI, it probably is not the primary cause of the initial decrease in GFR in myoglobinuric AKI. Rather than high intratubular pressures from obstructing casts, intratubular pressures were found to be low in the glycerol-induced model of AKI.[35] This observation was interpreted to indicate that the presence of casts is the result, rather than the cause, of the decrease in GFR and urine flow. Instead of causing the initial decrease in renal function, cast formation may play a role in the maintenance of the renal failure once it develops.[56]

Glomerular Fibrin Deposition. Because of the liberation of tissue factors, both rhabdomyolysis and intravascular hemolysis can initiate disseminated intravascular coagulation (DIC).[19] Fibrin strands have been demonstrated in glomeruli from patients[57] and experimental animals[58] with rhabdomyolysis-induced AKI. Intravenous infusion of a muscle extract in rabbits resulted in DIC, renal dysfunction, and glomerular microthrombi, whereas an intravenous infusion of pure myoglobin had no untoward effect.[59] This led to the conclusion that myoglobin, per se, is not the primary cause of the coagulation cascade activation in the crush syndrome, but rather it is the release of other muscle constituents that induces DIC and the subsequent deposition of glomerular microthrombi that are responsible for rhabdomyolysis-induced AKI.

Clinical and Laboratory Features of Rhabdomyolysis and AKI

The diagnosis of myoglobinuria can be suspected from a history and physical examination. However, the clinical features of rhabdomyolysis are nonspecific and the course of the syndrome is quite variable depending on the underlying cause and the general condition of the patient. The syndrome has local as well as systemic features and early or late complications may occur. Because the prompt recognition of rhabdomyolysis is critical to preventing late complications, all suspected cases must undergo a complete clinical inquiry, observation, and laboratory follow-up.

Risk Factors for Acute Kidney Injury. The frequency of AKI in the setting of rhabdomyolysis is unknown, and reports of frequency have ranged from 13% to 50%.[1] Gabow and colleagues[17] emphasized that no single laboratory value could predict which patients are at high risk for the development of AKI. However, using discriminant analysis, patients could be separated into high- and low-risk groups, with the high-risk group (elevated serum potassium and creatinine and reduced serum albumin concentrations) having a 41% prevalence of AKI.

Based on a large historical cohort (157 patients), Ward[60] identified clinical and laboratory differences between those patients in whom renal failure did or did not develop, and factors predictive of progression to renal failure. As shown in Table 36.2, patients with rhabdomyolysis and renal failure were older, had a higher incidence of hypertension, and were more hypotensive and volume depleted. A significantly greater proportion of them had a creatine kinase level greater than 16,000 IU per liter, although elevations to this degree were seen in 10.7% of patients in whom renal failure did not develop (Table 36.3). The renal failure group also had significantly higher serum potassium and phosphorus levels and lower serum calcium and albumin concentrations, and was more acidemic with a concomitant lower urinary pH. Sepsis, burns, and drug ingestion were the causes of rhabdomyolysis more closely associated with the development of renal failure. Using multiple logistic regression analysis, a scoring system was developed predicting the risk of renal failure in patients with rhabdomyolysis based on the variables of serum phosphorus, potassium, albumin, and creatine kinase concentrations, and the presence of volume depletion and sepsis. A point score of 7 or higher predicted a greater than 50% likelihood for the development of renal failure. In a multivariate analysis of 72 consecutive patients with rhabdomyolysis due to illicit

36.2 Univariate Analysis of Clinical Variables in Patients with Rhabdomyolysis Developing and Not Developing Renal Failure

Variables	Group		
	Renal Failure (N = 26)	Nonrenal Failure (N = 131)	P[a]
Age, year (SD)	53.7 ± 20.6	41.4 ± 18.1	0.002
Male (%)	69.2	61.1	0.418
Hypertension (%)	46.2	22.9	0.026
Diabetes mellitus (%)	11.5	7.6	0.562
Previous renal disease (%)	19.2	3.8	0.051
Dehydration (%)	38.5	4.6	0.001
Hypotension (%)	34.6	14.5	0.040
Nephrotoxin exposure (%)	19.2	39.7	0.020
Diuretic use (%)	30.8	16.8	0.147
Nonsteroid drug use (%)	19.2	6.1	0.101
IV hydration (%)[b]	80.7	54.2	0.289
Osmotic treatment (%)	26.9	22.9	0.674
Bicarbonate treatment (%)	50.0	12.2	0.001

[a]The P value for difference in means or proportions between renal failure and nonrenal failure groups.
[b]Greater than 150 mL per hour averaged over the first 24 hours after admission. SD, standard deviation; IV, intravenous.

drug use, patients with a creatine kinase level greater than 25,000 IU per liter, hypotension, and leukocytosis were at a greater risk of developing AKI, whereas hyperthermia (temperature >38.5°C) was associated with a reduced risk.[61] This association does not indicate that hyperthermia is protective against rhabdomyolysis, rather it is most likely due to earlier presentation to, or evaluation or fluid resuscitation in the emergency department.

Urinalysis. Examination of the urine provides the first laboratory clue to the presence of myoglobinuria. Classically, the initial urine is dark (Table 36.4) and usually with an acid pH; the benzidine or orthotoluidine reagent gives a positive reaction for blood (3+ to 4+), but microscopic examination of the urinary sediment fails to reveal any red blood cells (RBCs). Specific tests for urine myoglobin determination are available in some clinical laboratories but, as noted earlier, urine myoglobin levels are not the most sensitive clinical markers for rhabdomyolysis. Although the strongest clinical clue for myoglobinuria is the presence of strongly heme-positive urine and the absence of RBCs, in one major series[17] hematuria was present in 32% and the dipstick was heme negative in 18% of the patients with rhabdomyolysis. In addition, proteinuria was detected by dipstick in 45% of patients,[17] which may be attributed to altered glomerular permeability or tubular transport of small proteins.[62] The urinary sediment demonstrates brown "debris" and, with the evolution of renal injury, pigmented brown granular casts and renal tubular epithelial cells are seen.

Serum Potassium Concentration. The most life-threatening consequence of rhabdomyolysis is the release of large amounts of intracellular potassium into the circulation. Given the crucial role that potassium plays in maintaining the homeostasis of resting membrane potential, it is evident that vital organs such as the heart are at greatest risk to sustain arrhythmogenic activity. This implies that an electrocardiographic follow-up is mandatory to monitor for potentially grave arrhythmias. Because more than 98% of total body potassium resides in cells, and skeletal muscle represents 60% to 70% of the total cellular mass, breakdown of even a small area of skeletal muscle releases a considerable potassium load. The presence of

36.3 Univariate Analysis of Laboratory Variables in Patients with Rhabdomyolysis Developing and Not Developing Renal Failure

Variables	Group		
	Renal Failure (N = 20)	Nonrenal Failure (N = 131)	p
Peak creatine kinase >16,000 IU/L, %	57.7	10.7	<0.001
Serum bicarbonate (mmol/L)	21.4 ± 7.2	23.7 ± 4.0	0.1306
Serum potassium (mmol/L)	4.73 ± 1.2	3.92 ± 0.6	0.0018
Serum phosphorus (mmol/L)	1.85 ± 1.08	0.06 ± 0.35	0.0006
Serum calcium (mmol/L)	2.02 ± 0.4	2.14 ± 0.2	0.1452
Serum albumin (g/L)	30.8 ± 10.0	35.9 ± 8.0	0.0107
Arterial pH	7.33 ± 0.10	7.38 ± 0.11	0.0495
Urinary pH	5.19 ± 0.06	5.75 ± 1.0	0.0009

All values are mean standard deviation except peak creatine kinase.

acidosis may shift more potassium extracellularly and worsen the hyperkalemia. As noted in the previous section on Risk Factors for AKI, admission serum potassium levels tend to be higher in patients who go on to experience AKI.[60] Approximately half of an acute potassium load is handled by renal excretion[63]; therefore, in AKI, serious hyperkalemia can result and is usually the major indication for dialysis.

Creatine Kinase. The classic laboratory finding of rhabdomyolysis is an elevated serum creatine kinase of at least five

36.4 Differential Diagnosis of Pigmenturia

Factors	Myoglobinuria	Hemoglobinuria	Porphyria
Urine color	Brown	Reddish brown	Dark red
Serum color	Clear	Pink	Clear
Orthotoluidine reaction	Positive	Positive	Negative
Watson-Schwartz porphobilinogen	Negative	Negative	Positive
Muscle pain/tenderness	Present	Absent	Absent
Serum creatine kinase level	Elevated	Normal	Normal
Serum haptoglobin	Normal	Decreased	Normal

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times the normal value, where the striated muscle isoenzyme (CK-MM) is predominately found. The serum half-life of creatine kinase (~36 hours) is much longer than myoglobin, which makes it a more reliable tool for diagnosis. Normal creatine kinase levels are 45 to 260 IU per liter. Following muscle injury, the level rises within 12 hours, peaks in 1 to 3 days, and declines 3 to 5 days after the cessation of muscle injury.[29] Although no correlation has been established between the absolute level of the creatine kinase and the risk for development of AKI, creatine kinase levels are significantly higher in patients in whom renal failure develops.[19,29] Following admission, changes in creatine kinase concentrations provide some insight into whether the rhabdomyolysis is worsening or resolving, and following levels is essential to observe for the "second wave" phenomenon (described later in this chapter).

Acid–Base Balance. The conditions that cause rhabdomyolysis involve tissue trauma or ischemia and predispose one to an augmented acid load. In a study by Ward,[60] patients with rhabdomyolysis who progressed to renal failure tended to be more acidemic. An elevated serum anion gap is usual in patients with rhabdomyolysis and due to the impaired renal excretion of intracellular organic acids released from damaged muscles, as well as a retention of inorganic anions such as phosphate.[64]

Uric Acid. Due to the release of intracellular purines from damaged myocytes, hyperuricemia is expected in patients with rhabdomyolysis, especially when the muscle injury is due to strenuous exercise or exertion.

Blood Urea Nitrogen: Creatinine Ratio. Both AKI and the increased release of creatine from damaged myocytes increase the serum concentrations of blood urea nitrogen (BUN) and creatinine. However, the rise in creatinine is more pronounced and, in turn, alters the normal 10:1 ratio of BUN to creatinine to a ratio of 6:1 or less. Based on creatine:creatinine kinetics and their respective concentrations in skeletal muscle, Oh[65] challenged this conventional view. He pointed out that the patient population in which rhabdomyolysis develops tends to have a larger percentage of younger men with a greater muscle mass, whereas other forms of AKI are more often associated with older and more cachectic patients who have less muscle mass and thus reduced creatinine production rates.

Calcium–Phosphorus Metabolism. The perturbations of calcium and phosphorus metabolism usually seen in most types of AKI appear to be exaggerated in rhabdomyolysis-induced AKI.[19,66] Following the destruction of muscle cells, the release of inorganic phosphorus into the plasma causes hyperphosphatemia[19,64] and subsequent hypocalcemia through the deposition of calcium phosphate in the destroyed muscle cells (dystrophic calcification) and other tissues. Hypocalcemia may be accentuated by the inhibition of renal vitamin D 1α-hydroxylase, which results in the downregulation of the production of the active form of vitamin D ($1,25[OH]_2D_3$). This observation may be explained by hyperphosphatemia, which is known to decrease synthesis of $1,25(OH)_2D_3$ and to stimulate the production of the parathyroid hormone.[64,67] A recent case report described elevated FGF23 levels in rhabdomyolysis-induced AKI and may provide a mechanism for the inhibition of renal 1α-hydroxylase.[68] Regardless of the mechanism, in the absence of frank tetany, hypocalcemia usually does not require treatment. In fact, correction of the hypocalcemia with vigorous intravenous calcium replacement may increase both dystrophic (calcium deposition in damaged muscle) and metastatic calcification due to the high serum PO_4 and the $Ca \times PO_4$ product.

Approximately 20% to 30% of patients with myoglobinuric AKI experience transient hypercalcemia during the recovery (diuretic) phase.[19,64] Early studies[69,70] suggested that hypercalcemia was due to the normal remobilization of calcium deposits in the injured muscle that occurs during the recovery phase of AKI. Alternatively, it has been proposed that as renal function improves, the combination of a decreasing serum phosphorus concentration and the ambient secondary hyperparathyroidism, secondary to hypocalcemia, stimulates the synthesis of $1,25(OH)_2D_3$ resulting in an "overshoot" hypercalcemia.[64] This augmented $1,25(OH)_2D_3$ production may be due, in part, to the release of vitamin D from damaged muscle tissue.[64,71]

Urinary Sodium Excretion. Impaired renal tubular reabsorption of sodium is typically seen in most types of oliguric AKI as manifested by a high fractional excretion of sodium. However, in both myoglobinuric and hemoglobinuric AKI, a low fractional excretion of sodium (<1%) has been observed[38] that resembles a prerenal azotemia during the early course. As noted earlier in this chapter, this phenomenon is most likely due to hypovolemia and vasoconstriction, which lead to renal hypoperfusion.

Disseminated Intravascular Coagulation. DIC is commonly present in patients with rhabdomyolysis and may be due to the release of intracellular thromboplastins that activate the clotting cascade.[63,64] Moreover, DIC may be an important factor in the pathogenesis of the AKI (see section on Glomerular Fibrin Deposition, previously).

Differential Diagnosis

Myoglobin-induced AKI should be suspected in patients with trauma presenting with the classic triad of heme-positive urine, an elevated serum creatine kinase level, and dark (pigmented) urine containing dirty-brown granular casts without RBCs. More subtle cases, usually associated with diffuse nontraumatic rhabdomyolysis, may be more difficult to detect. The differential diagnosis of pigmenturia is limited (Table 36.4). Although certain drugs may impart an orange, red, or brown hue to the urine such as rifampin and nitrofurantoin, they do not react with the benzidine or orthotoluidine reagent on the urine dipstick. Porphyrins also color the urine brown

but do not react to give a positive test for occult blood. The most difficult challenge is to discriminate myoglobin from hemoglobin in the urine. Because these are heme proteins, they both react with the benzidine or orthotoluidine reagent and both are associated with the absence of RBCs in the urine sediment. One helpful clue may be the color of the serum in these two conditions. Because myoglobin is relatively rapidly cleared by the kidney, serum levels of myoglobin are not sufficiently elevated to alter the color of the serum in patients with rhabdomyolysis. In contrast, because of its much larger size and its avid binding to haptoglobin, hemoglobin is not as rapidly cleared by the kidney and serum levels may be high enough to result in a pink discoloration of the serum in patients with hemoglobinuria.

Clinical Course and Complications of Myoglobinuric Acute Kidney Injury

Myoglobinuric AKI can run a course ranging from mild renal dysfunction with only transient oliguria and rapid recovery to a much more catastrophic disease requiring frequent dialysis for periods of 2 or 3 weeks. Typically, the duration of oliguria is 7 to 10 days; during this interval a period of anuria may exist for up to 3 days. Resumption of more normal urine formation heralds the recovery of renal function as patients enter the diuretic phase with a subsequent clearing of azotemia and the cessation of the requirement for hemodialysis.

In addition to muscle injury and AKI, patients with rhabdomyolysis may have peripheral neuropathies. These can result from compartment syndromes in which involved muscles become edematous in confined tissue spaces with compromise of blood supply to both muscle and nerves in the area.[69] Measurement of tissue pressure has been advocated as a tool in identifying those areas of damaged muscle at risk, and a surgical fasciotomy may be required to avoid this complication.[64] Swelling of the muscles can lead to impairment in the blood supply of the muscles, resulting in a recurrence or "second wave" of muscle necrosis, as reflected by a second rise in the serum creatine kinase concentration. Neuropathy also can result from traction if rhabdomyolysis is caused by prolonged coma, as from drug overdose.[64]

Prevention and Treatment of Myoglobinuric Acute Kidney Injury

Understanding the possible mechanisms by which rhabdomyolysis causes AKI can provide the basis for the various therapies advocated for this disorder. If possible, treatment of the underlying condition is a priority. Given the pathogenic nature of hypovolemia, renal hypoperfusion and, based on experimental and clinical data, early intravascular volume expansion by intravenous administration of NaCl 0.9% is essential to restore RBF, maintain GFR, and ultimately prevent AKI.[64,72] Because myoglobin is more nephrotoxic at an acid pH, most groups advocate alkalinization of the urine with sodium bicarbonate.[64,72,73] By correcting cellular acidosis, bicarbonate therapy may reduce renal tubular epithelial swelling and attenuate renal tubular and vascular collapse.[74] There is a theoretical concern that inducing a metabolic alkalosis with such treatment may enhance metastatic calcification, but the salutary benefit of bicarbonate therapy probably outweighs any untoward effect.

Following the repletion of volume and the production of urine within an acceptable range, the patient could undergo forced diuresis. Mannitol has long been recognized to be an effective agent in the prophylaxis against the development of experimental and clinical AKI, in particular when there is suspicion of compartment syndrome. However, recent studies have shown that the administration of NaCl 0.9% in combination with mannitol is not more effective in the prevention of AKI than the administration of NaCl 0.9% alone. Furthermore, mannitol can cause AKI and should be used with caution.[75]

Furosemide, a loop diuretic, has the theoretic advantage of inhibiting sodium transport in the thick ascending limb of the Henle loop. Oxygen consumption is dictated primarily by the rate of sodium transport, and a precarious balance exists in this segment between the rate of oxygen delivery and its consumption.[76] By inhibiting sodium transport, furosemide may reduce oxygen consumption in the face of limited delivery and thereby preserve cell viability. In addition, the augmented urinary flow induced by the diuretic may reduce the risk of tubular obstruction. However, loop diuretics can cause increasing acidification of the urine, worsening intravascular volume depletion, and can induce ototoxicity, and thus the use of these agents has not been generally recommended.[77]

Although there are no controlled trials to show a direct benefit of a "mannitol-bicarbonate cocktail" in the prevention of AKI in rhabdomyolysis, there are case reports suggesting such therapy was instrumental in averting renal injury.[78,79] Adequate fluid hydration and bicarbonate therapy, however, did not ameliorate the development of renal failure in a large retrospective study.[60] Moreover, in a retrospective evaluation of 382 intensive care unit trauma admissions with a creatine kinase of >5,000 IU per liter, the use of bicarbonate and mannitol in 40% of this group had no effect on rates of renal failure, the need for dialysis, and mortality, although there was a trend to a lower mortality rate in patients with creatine kinase greater than 30,000 IU per liter who were treated with bicarbonate and mannitol.[80] This may provide a window of therapeutic potential for patients with extremely high levels of creatine kinase. Initially, the optimization of intravascular fluid volume deficits should be carried out with dispatch using isotonic crystalloid solutions, usually normal saline. Variables useful in following this course of therapy include a physical examination of the state of the circulation and hematocrit, and the recording of external fluid balance. If the clinical assessment suggests that a euvolemic state has been achieved but no improvement in oliguria has occurred, a decision must be made about further intervention. Usually by this time, laboratory results offer further support for the diagnosis of myoglobinuria and acute renal insufficiency, and we recommend the prompt infusion of a mannitol–bicarbonate solution. This is made by adding two ampules, each containing 12.5 g mannitol in 50 mL, and two ampules of 50 mEq $NaHCO_3$ in 50 mL to 800 mL of 5% dextrose

in water (D5W) for intravenous infusion. This reconstituted liter is roughly isosmotic with plasma once the glucose is metabolized and contains both mannitol and 100 mEq $NaHCO_3$. It should be infused at 250 mL per hour; urine flow rate should increase by the end of the 4-hour infusion if the treatment is successful. If this is the case, the solution should continue to be administered at a rate equal to urine output and sufficient to achieve a urine pH greater than 6.5 until such time as azotemia has started to clear and all evidence of myoglobinuria has disappeared. If urine flow does not increase after the 4-hour infusion, the patient has entered the established phase of oliguric renal failure and should be treated conservatively until dialysis can be arranged based on conventional indications. This approach corrected oliguria, hastened the clearing of azotemia, and avoided the need for dialysis in roughly half of patients with myoglobinuric AKI.[79] As a group, these patients had somewhat lower indices of muscle damage and somewhat better preservation of renal function than the half that did not respond. Whether this reflects the earlier intervention or a less severe degree of muscle injury, or both, is not known, and it is also possible that vigorous volume expansion with normal saline alone might have caused the same result in some patients. Given that complications from the mannitol–bicarbonate infusion are few, even in those patients who do not respond, its use should be seriously entertained in patients with myoglobin-induced AKI.

When AKI has become established, dialysis must be used. Early and intensive hemodialysis may be associated with significantly lower morbidity and mortality rates.[64,81] Experience with peritoneal dialysis indicated that solute clearance using this modality was inadequate to keep pace with the rapid rate of solute appearance in these highly catabolic patients,[82] and thus, hemodialysis should be the modality of treatment. Even so, daily hemodialysis often is required for the first several days until the consequences of extensive muscle injury have abated and rates of urea and potassium accumulation have fallen. Thereafter, a schedule of thrice-weekly dialysis usually is adequate unless other factors, such as continued catabolism from infection or surgical wound débridement, or volume overload from parenteral nutritional therapy demand more frequent treatments. Although the overall prognosis for the renal failure is favorable, the ultimate prognosis for the patient probably depends more on other coexisting conditions such as sepsis, bleeding, and respiratory failure.

Hemoglobinuric Acute Kidney Injury

During most types of extravascular hemolysis, the released hemoglobin is quickly taken up by the reticuloendothelial system and metabolized to bilirubin. Thus, extravascular hemolysis rarely results in AKI. On the other hand, due to the binding capacity of haptoglobin, which effectively sequesters free hemoglobin, and advances in blood bank technology that prevent massive intravascular hemolysis from mismatched blood transfusions, the frequency of hemoglobinuric AKI is an uncommon event compared to myoglobinuric AKI.

Causes of Hemoglobinuria

Hemoglobinuria results from the filtration of free hemoglobin in plasma, due almost exclusively to intravascular hemolysis, which occurs in a variety of conditions (Table 36.5). Although each of the listed causes may be associated with acute renal dysfunction, hemoglobinuria is more likely

36.5 Causes of Hemoglobinuria and Acute Kidney Injury

Genetic defects Glucose-6-phosphate dehydrogenase deficiency Paroxysmal cold hemoglobinuria March hemoglobinuria
Infection Malaria Clostridia
Transfusion reactions
Chemical agents Arsine copper sulfate poisoning Glycerol Quinine sulfate Analine Benzene Hydralazine Fava beans Cresol Sodium chlorate Methyl chloride Coal tar products
Venoms Rattlesnake, copperhead, water moccasin, coral snake Tarantula Brown recluse spider
Traumatic/mechanical destruction Prosthetic valves Disseminated intravascular coagulation Extracorporeal circulation
Miscellaneous
Heat stroke
White phosphorus
Hemoglobin infusions

Reprinted from Dubrow A, Flamenbaum W. Acute renal failure associated with myoglobinuria and hemoglobinuria. In: Brenner BM, Lazarus JM, eds. Acute Renal Failure, 2nd ed. New York: Churchill Livingstone; 1988:285, with permission.

to occur in only a few settings. These include hemolytic transfusion reactions, DIC, march hemoglobinuria, glucose-6-phosphate dehydrogenase deficiency, and infections with clostridia and Plasmodium falciparum malaria, the latter causing blackwater fever.[83]

Hemoglobin Physiology and Metabolism

Hemoglobin has a molecular weight of 68,000 Da and is a tetramer of two α and two β globin chains surrounding a ferrihemate core. As noted earlier, free hemoglobin in plasma is tightly bound to haptoglobin, and the hemoglobin–haptoglobin complex is too large to be filtered by the glomerulus. Thus, free hemoglobin appears in the urine only after the plasma concentration of hemoglobin exceeds the maximum binding capacity of haptoglobin, which is approximately 100 mg per deciliter (in contrast to 1.5 mg per deciliter for myoglobin). In the setting of intravascular hemolysis, the relatively low renal clearance of hemoglobin (fractional clearance relative to inulin, 0.03) results in an increase in plasma hemoglobin levels sufficient to be visible to the naked eye as pink-colored plasma, whereas with rhabdomyolysis, the rapid renal clearance of myoglobin (fractional clearance, 0.75) prevents myoglobin retention in the plasma, and the plasma color is not visibly altered. The color of the plasma is an important "bedside" clue that helps to distinguish between these two forms of pigmenturia.

Clinical and Laboratory Features of Hemoglobinuric Acute Kidney Injury

Because both myoglobin and hemoglobin are heme-containing proteins, and the heme moiety has been implicated as a major factor in inducing renal injury, it is generally accepted that the mechanisms by which they both cause nephrotoxicity are similar. Moreover, in the clinical settings, most commonly associated with it other pathogenetic mechanisms have been proposed to account for the AKI. For example, with hemolytic transfusion reactions, the interaction of antigens on the red cell stroma with preformed antibodies may be responsible for adverse effects on kidney function.[84] In DIC, afferent arteriole and glomerular capillary fibrin deposition are the events most directly related to AKI.[85] March hemoglobinuria occurs from the traumatic hemolysis of RBCs, most likely in people with a genetic susceptibility[83]; AKI in this setting results from a volume depletion as well as hemoglobinuria. In blackwater fever, hemolysis is caused by the abrupt release of P. falciparum trophozoites and perhaps also from the quinine used to treat it.[86] These patients are dehydrated, volume depleted from sweating, and have high fevers. Clostridial sepsis also has multiple effects on renal function including hypotension, acidosis, and DIC, as well as hemolysis.[87]

Laboratory features of intravascular hemolysis and hemoglobinuria include (1) increased serum lactate dehydrogenase (LDH) levels, (2) low serum haptoglobin levels, (3) increased unconjugated (indirect) serum bilirubin, (4) increased reticulocyte count, and (5) hyperkalemia.[83] As with myoglobinuria, hemoglobinuria and hemoglobinuric AKI are associated with pigmented urine casts. The differential diagnosis and clinical course of hemoglobin-induced AKI are similar to those described for myoglobinuria.

Prevention and Treatment of Hemoglobinuric Acute Kidney Injury

The prevention of hemoglobinuric AKI involves many of the same preventive measures for myoglobinuric AKI, such as correcting the volume depletion and the administration of bicarbonate. In fact, Bywaters' therapy to treat crush injuries using saline and bicarbonate in the 1940s was based on earlier reports demonstrating such therapy was beneficial in preventing renal failure in mismatched blood transfusion reactions.[88] Interestingly, in an experimental animal model of hemoglobinuric AKI, the simultaneous administration of the amino acid, lysine, prevented the development of AKI. This was attributed to the ability of lysine to inhibit proximal tubular reabsorption of hemoglobin or its heme moiety.[89] The clinical use of such therapy remains to be determined.

The management of sustained AKI usually requires hemodialysis. These patients, in general, are less catabolic than patients with rhabdomyolysis. The AKI usually lasts 1 to 2 weeks, but full recovery of renal function is often the case.

CRYSTAL-INDUCED ACUTE KIDNEY INJURY

Uric Acid Nephropathy

Acute uric acid nephropathy is the term given to the development of AKI caused by renal tubular obstruction by urate and uric acid crystals. The main clinical setting in which uric acid nephropathy occurs is the treatment of malignancy, especially of leukemia and lymphoma. Treatment of these malignancies results in cell death and the release of large amounts of uric acid precursors. Some patients with these malignancies also have renal insufficiency and high serum uric acid levels before chemotherapy, possibly because of early uric acid nephropathy and the rapidly dividing cell population.[90]

Properties of Uric Acid

The final breakdown product of purine degradation in humans is uric acid (Fig. 36.2). Most other mammals degrade purines to the soluble end product allantoin, but humans lack the enzyme uricase. Uric acid (2,6,8-trioxypurine) is a weak acid with a pK_a of 5.75. Urates are the ionized form of uric acid, and at a physiologic pH of 7.4, over 95% of uric acid dissociates into urates, with 98% existing as monosodium urate. However, uric acid predominates in acidic urine. Although initial in vitro and in vivo studies had shown urate binding to plasma proteins, urate binding to human serum proteins probably is not significant.[90]

At a temperature of 37°C and a plasma pH of 7.40, the saturation point of urate is at a concentration of 8.8 mg per deciliter, which is only slightly above the normal physiologic range

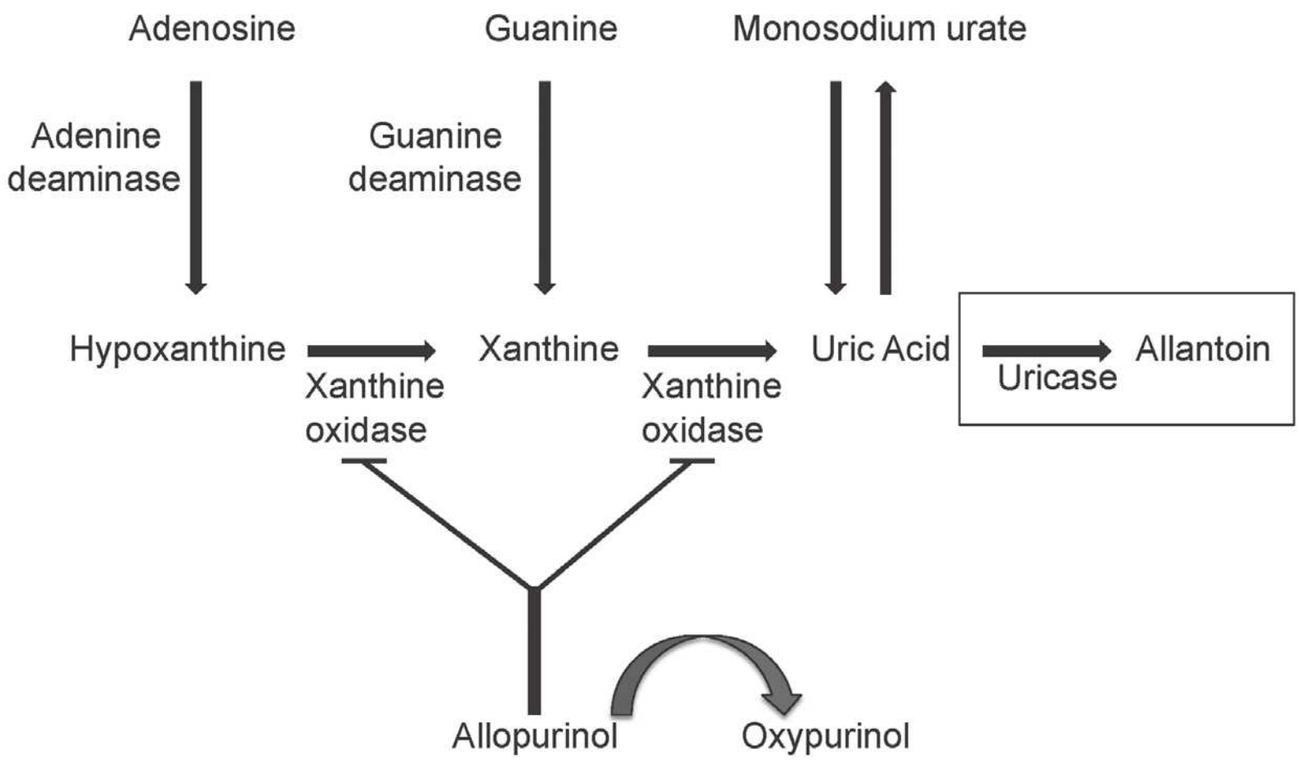

FIGURE 36.2 The pathway of purine degradation showing the competitive inhibition of urate formation by allopurinol and the site of action of rasburicase. The conversion of uric acid to allantoin by uricase (urate oxidase) does not occur in humans.

in humans.[91] However, urate crystal precipitation in the bloodstream does not occur even with concentrations much higher than the saturation point. On the other hand, the precipitation of urate occurs in extracellular fluid when the solubility concentration is exceeded. The most important factor affecting the solubility of uric acid is pH. For example, in a buffer medium at a pH of 5.0, saturation with uric acid occurs at a concentration below 10 mg per deciliter, whereas at a pH above 7.0, saturation occurs at a concentration above 150 mg per deciliter.[91]

There are four components to the renal handling of urate (Fig. 36.3). First, urate is filtered freely at the glomerulus. Virtually all of this filtered urate is then reabsorbed in the proximal tubule. An amount equal to 50% is then secreted, and after further absorption, 10% is finally excreted.[92] In humans, there is net reabsorption of urate with the fractional excretion of urate being approximately 10%.[93] Animal micropuncture studies have localized the primary nephron site of urate absorption and secretion to the proximal tubule. An anion exchanger and a voltage-dependent pathway seem to be the mechanisms involved in urate transport.[93]

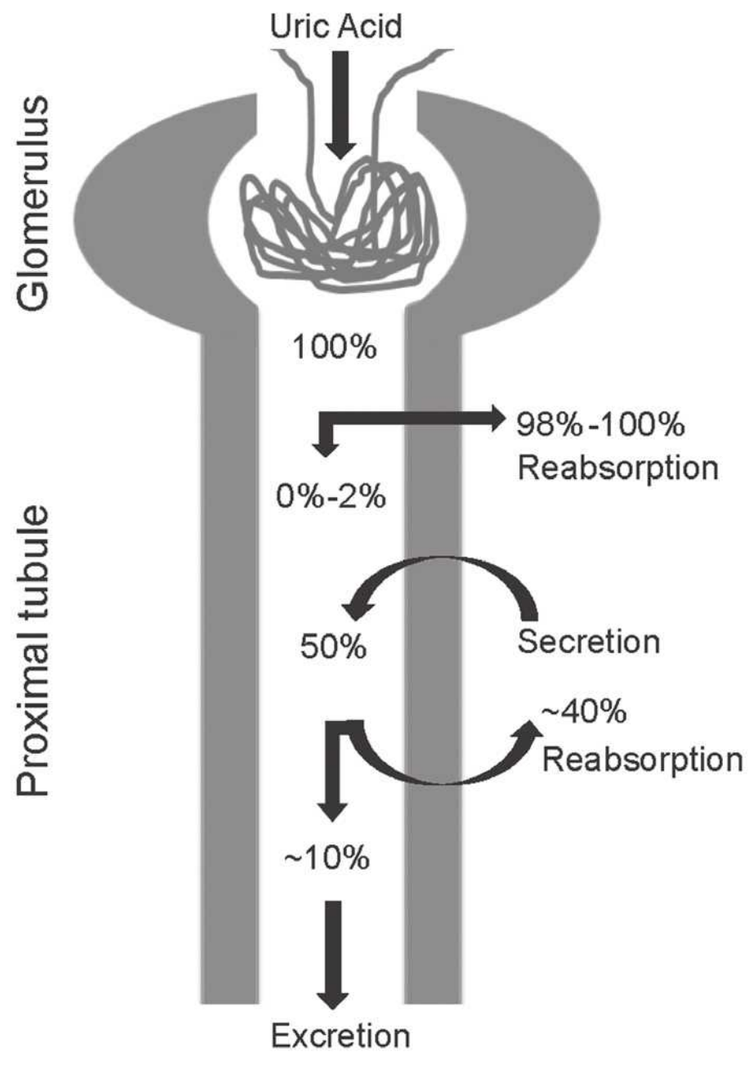

FIGURE 36.3 The renal elimination of uric acid. A four-component model of renal uric acid handling.

Pathogenesis of Uric Acid Nephropathy

Experimental animal models of uric acid nephropathy are characterized by hyperuricemia, hyperuricosuria, and uric acid deposits in and dilation of the kidney tubules, as observed in the clinical entity.[93] Along with the presence of extensive distal tubule deposits of uric acid and urate, micropuncture studies in the rat have shown increased proximal and distal tubular pressures. The vasa recti also show deposits, and efferent arteriolar and peritubular capillary pressures also are increased.[94]

Humans with malignancies and hyperuricemia have an increased urinary excretion rate and urinary concentration of uric acid both in the presence and absence of renal insufficiency.[90] Autopsy studies have documented the presence of uric acid crystals in patients with leukemia. The uric acid crystals were found only within the lumens of renal tubules, in contrast to patients with gout, in whom no uric acid crystals were found in tubular lumens.[95,96] In addition, internal hydronephrosis has been described in association with the intraluminal uric acid crystals, but the glomeruli and tubules usually are intact.[97] Supporting the concept that mechanical intraluminal obstruction causes uric acid nephropathy are the observations that the renal failure reverses after a short time and that there is earlier and greater depression of inulin clearance compared with p-aminohippurate clearance.[97] This evidence is consistent with the concept that uric acid nephropathy occurs because of uric acid crystals obstructing the renal tubular segments with maximum acidifying and concentrating abilities, namely, the distal tubule and the collecting duct. The obstruction then leads to increased intraluminal pressure, decreased filtration pressure, and a reduction in GFR.

Clinical and Laboratory Manifestations

The initial reports of uric acid nephropathy focused on patients treated for acute lymphoblastic leukemia, 10% of whom had uric acid nephropathy.[90,97] In these early patient series, risk factors for uric acid nephropathy included urine pH less than 5.0, dehydration, rapid response to chemotherapy, elevated serum uric acid, increased urinary excretion of uric acid, and preexisting renal insufficiency.[97] Tumor lysis syndrome and acute uric acid nephropathy develop primarily during the treatment of leukemia and lymphoma, but can also occur in association with the treatment of other types of malignancies or in other situations associated with elevated plasma levels and the urinary excretion of uric acid. Multiple other nonhematopoietic neoplasms have been reported to cause acute uric acid nephropathy and tumor lysis syndrome.[90] Hyperuricemic AKI also has been reported after epileptic seizures, during pregnancy, following heat stress, and in the setting of cyclosporine use and renal transplantation.[98–100]

Uric acid nephropathy during tumor lysis syndrome is characterized by elevations in serum urea nitrogen, creatinine, potassium, uric acid, and phosphate concentrations, and by a decrease in the serum calcium concentration. Hyperuricemia before chemotherapy occurs in 30% to 50% of patients with leukemia and lymphoma, and renal insufficiency seems to be more common in patients with hyperuricemia before chemotherapy.[90] The uric acid levels are now routinely normalized with allopurinol, alkalinization, and diuresis prior to the initiation of chemotherapy.[90] Patients receiving chemotherapy are at risk for other forms of renal failure in addition to acute uric acid nephropathy, and the urinary uric acid-to-creatinine ratio is a useful test to differentiate these various forms of renal failure. A ratio greater than 1 is consistent with acute uric acid nephropathy.[90] This is supported by the observation that both the serum uric acid concentration and the urinary excretion of uric acid are elevated in acute uric acid nephropathy as opposed to other forms of renal failure, where serum uric acid concentrations may be high but urinary excretion is not elevated.[101] The urinary uric acid-to-creatinine ratio is more helpful in the diagnosis of uric acid nephropathy than urinalysis, which usually is nondiagnostic. The urine sediment may be normal or may occasionally reveal amorphous material containing uric acid crystals.[90] Uric acid crystals appear as needle-shaped, negative birefringent crystals or as microcrystallites (Fig. 36.4A,B).

Elevations in BUN and serum creatinine typically develop 2 days after the initiation of chemotherapy, with a return to baseline after 7 to 10 days. Prior renal insufficiency seems to predispose one to the development of uric acid nephropathy.[102] The AKI is usually of the oliguric variety, even when treated with diuretics.[102] When indicated, one to four dialysis treatments are usually sufficient before the spontaneous return of renal function.[102]

As noted previously, the electrolyte abnormalities associated with the tumor lysis syndrome and uric acid nephropathy are hyperkalemia, hyperphosphatemia, and hypocalcemia. These abnormalities result from the release of intracellular contents after tumor necrosis, and patients with large tumor burdens are at higher risk for tumor lysis syndrome.[90] Hyperkalemia actually occurs in less than 5% of patients after chemotherapy, but if it develops, it can occur within 24 hours of the initiation of chemotherapy and can be severe enough to necessitate emergent dialysis. In fact, sudden death has been reported as a consequence of tumor lysis–induced hyperkalemia, occurring within 48 hours of chemotherapy.[103] Hyperkalemia also is more likely to occur in patients with preexisting renal insufficiency.[102]

Hyperphosphatemia, on the other hand, is very common in the tumor lysis syndrome and occurs in virtually all patients in whom AKI develops and in 30% of patients with normal renal function.[90] The development of hyperphosphatemia also is correlated with the tumor burden. In patients with renal failure, the phosphorus concentrations average 12 mg per deciliter with a range of 7 to 22 mg per deciliter.[90,102] Hypocalcemia also is common, and the development of hypocalcemia correlates with hyperphosphatemia.[90] In the presence of hyperphosphatemia, the etiology of hypocalcemia may be the precipitation of calcium phosphate salts, as discussed in the section on Myoglobinuric Acute Kidney Injury, discussed previously. When this occurs in the kidney, it may contribute to the AKI seen in tumor lysis syndrome.[104] Hyperphosphatemia also may contribute to the development of hypocalcemia by depressing the production of $1,25(OH)_2D_3$. Hyperphosphatemia has been shown to worsen experimental AKI but the mechanism is not clear because calcium phosphate deposition could not be demonstrated in animal models.[105] Calcium deposits have been found at an autopsy in the calyces and tubules of a patient who had AKI in association with tumor lysis syndrome, hyperphosphatemia (20 mg per deciliter), and hypocalcemia.[106]

Despite these characteristic manifestations of tumor lysis syndrome, it is difficult to predict in which patients acute uric acid nephropathy will develop. Even when appropriate prophylactic measures are taken with hydration, alkalinization, and allopurinol, the following still may develop: hyperuricemia in 9%, hyperphosphatemia in 25% to 50%, hypocalcemia in 10% to 60%, and hyperkalemia in 8%. However, the incidence of clinically significant tumor lysis syndrome after chemotherapy is only 5%.[90] The likelihood for the development of acute uric acid nephropathy is increased in the presence of renal insufficiency, in patients with oliguria before therapy, and in patients with lymphoma with high serum LDH levels.[102,107]

Differential Diagnosis

The diagnosis of acute uric acid nephropathy should be suspected when AKI, in concert with tumor lysis syndrome, develops within the first 1 to 3 days after the initiation of chemotherapy for lymphoma or leukemia. The diagnosis sometimes is made difficult by the variety of drugs, radiographic studies requiring contrast exposure, and the associated clinical problems common during the early presentation of malignancies. Renal complications associated with

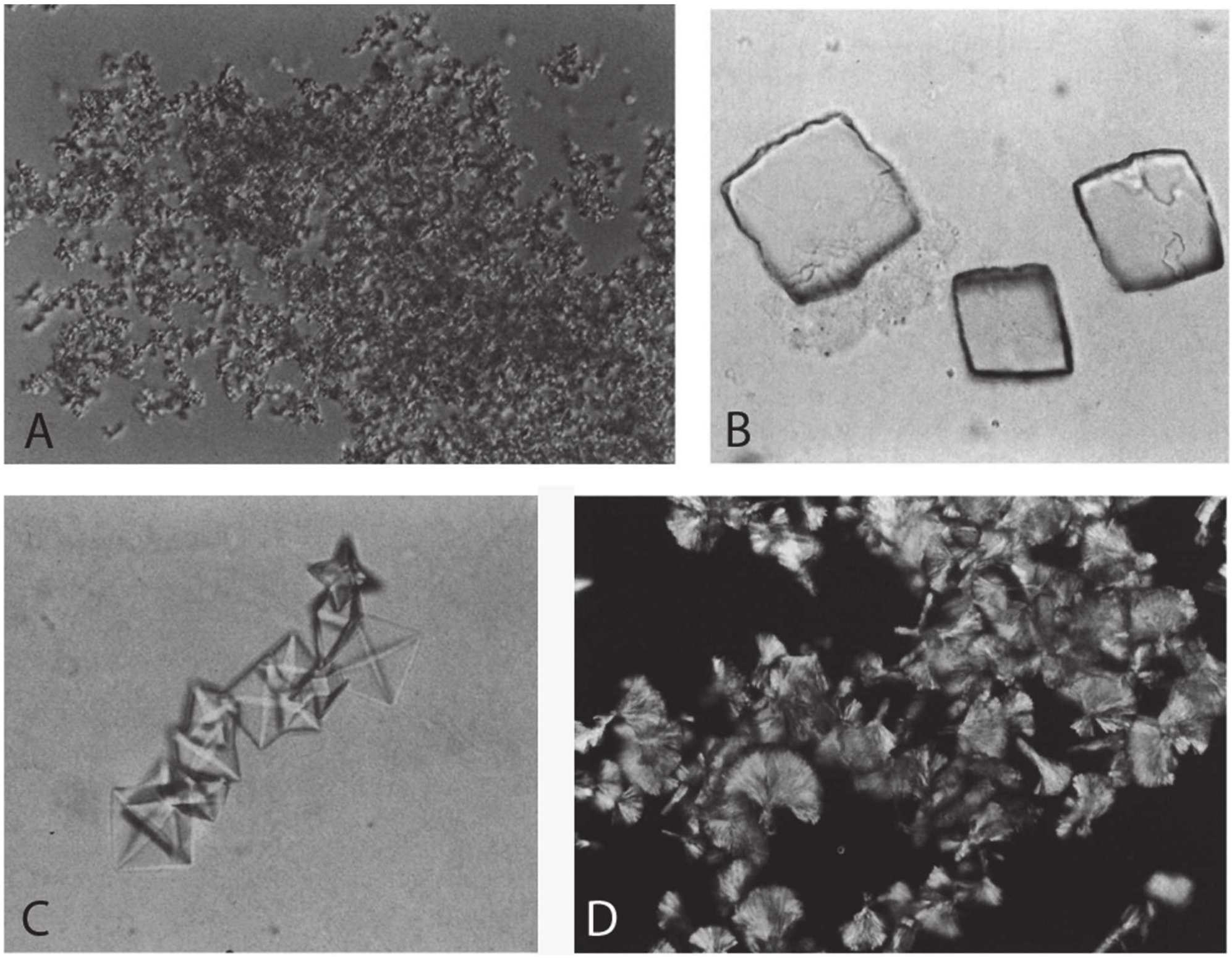

FIGURE 36.4 **A:** Amorphous urate crystals in urine. (Interference contrast microscopy, magnification ×200.) **B:** Uric acid crystals, cuboidal shape. (Magnification ×160.) **C:** Envelope-shaped calcium oxalate dihydrate form of crystal. (Note: Needle-shaped monohydrate calcium crystals are not pictured.) **D:** Sulfadiazine crystals in urine. (Polarized microscopy, magnification ×40.) These birefringent crystals often assume a "fan" or "sheaf of wheat" shape. (Courtesy of Professor M. H. Haber, Department of Pathology, Rush Medical College, Chicago, IL.)

malignancies include direct lymphomatous or leukemic renal infiltration, obstruction due to stones, and obstruction due to malignancy (summarized in Table 36.6). However, despite the common occurrence of direct lymphomatous or leukemic renal infiltration, it rarely causes AKI.[102]

Spontaneous hyperuricemia occurs more commonly with lymphomas, and some patients present with renal insufficiency before treatment, possibly because of uric acid nephropathy.[90] Ultimately, the diagnosis of acute uric acid nephropathy is made in the presence of tumor lysis syndrome with the urinary uric acid-to-creatinine concentration ratio greater than 1 and with the exclusion of other causes of AKI.

Prophylactic Measures and Treatment

Before the dialysis era, the mortality rate from AKI associated with uric acid nephropathy was 50%, but with modern treatment, including proper prophylaxis and dialysis, uric acid nephropathy is rare, but when it does occur the prognosis for the AKI is excellent.[90] The treatment approach to uric acid nephropathy is divided into two stages. The first is to prevent or minimize the metabolic consequences of the tumor lysis syndrome, and the second is to treat these consequences when they do occur (Table 36.7). The approach to both prophylaxis and the treatment of tumor lysis syndrome includes the inhibition of xanthine oxidase, forced diuresis, and urinary alkalinization. When these measures fail to prevent the consequences of tumor lysis, and AKI from uric acid nephropathy develops, dialysis must be initiated to treat uremia and severe electrolyte problems, and to control hyperuricemia. However, rasburicase, a recombinant form of urate oxidase, is an additional option for patients with AKI from uric acid nephropathy and in patients with a high risk to develop tumor lysis syndrome (see the following).[108]

36.6 Acute Renal Complications Associated with Malignancies

Prerenal
Extracellular fluid depletion (poor intake, vomiting, diarrhea, hypercalcemia)
Hepatorenal syndrome (veno-occlusive disease, hepatic resection)
Drugs (calcineurin inhibitors, nonsteroidals)
Intrinsic
Glomerular Membranous nephropathy Amyloidosis (multiple myeloma) Pamidronate-associated collapsing Glomerulopathy (incidence unknown) Light-chain deposition disease
Tubulointerstitial Acute tubular necrosis (toxic/ischemic) Lymphomatous infiltration of the kidney Light-chain deposition disease Drugs (cisplatin, ifosfamide) Intravenous contrast Cast nephropathy (multiple myeloma)
Vascular Thrombotic-thrombocytopenic purpura/ hemolytic uremic syndrome (post-HCT, gemcitabine, mitomycin C) Tumor infiltration (renal cell carcinoma with renal vein thrombosis)
Postrenal
Intratubular obstruction
Uric acid nephropathy
Methotrexate
Cast nephropathy (multiple myeloma)
Extrarenal obstruction
Bladder outlet, ureteral (primary disease, retroperitoneal lymphadenopathy, retroperitoneal fibrosis)

HCT, hematopoietic cell transplant.
Reprinted from Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol. 2005 Jan;16(1):151–161, with permission.

36.7 The Approach to Uric Acid Nephropathy and Tumor Lysis Syndrome

Approach to prophylaxis for tumor lysis syndrome and uric acid nephropathy
Patients presenting prior to chemotherapy with hyperuricemia and evidence of a large tumor burden: allopurinol, 300–600 mg 4–5 L/24 hr of normal saline. Add diuretics if the patient is well hydrated and not maintaining an adequate urine output. If there is no response to diuretics, match fluid input with urine output. Urinary pH should be maintained above 7.0 by titrating intravenous bicarbonate therapy. Start with 100 mEq/L of sodium bicarbonate in D5W per hour. Bicarbonate therapy should be discontinued after serum uric acid is normalized. If clinically feasible, postpone chemotherapy until uric acid is normalized along with any other electrolyte abnormalities.
Patients presenting prior to chemotherapy and with a normal uric acid level but still at risk for tumor lysis syndrome: Allopurinol, 300–600 mg 4–5 L/24 hr of normal saline as described If clinically feasible, postpone chemotherapy until 2 days after start of allopurinol
Treatment of uric acid nephropathy and tumor lysis syndrome
Hemodialysis initiated per the routine indications including hyperkalemia, acidosis, hyperphosphatemia, volume overload, or uremia. Hemodialysis for control of hyperuricemia unresponsive to the previous measures. Adjust allopurinol doses for renal failure:

Creatinine clearance	Allopurinol dose
0	100 mg q3d
10	100 mg q2d
50	200 mg qd

After hemodialysis, supplement with 50% of allopurinol dose.
D5W, 5% dextrose with water; q3d, every 3 days; q2d, every 2 days; qd, every day.

Inhibition of Xanthine Oxidase. Allopurinol is a substrate for and a competitive inhibitor of the enzyme xanthine oxidase (Fig. 36.2). It blocks the conversion of hypoxanthine and xanthine to uric acid resulting in a reduction in both serum uric acid concentration and a urinary excretion of urates. In the presence of allopurinol, hypoxanthine and xanthine accumulate instead of uric acid, and the urinary excretion of these precursors also increases.[109] Hypoxanthine is highly soluble and even with increased renal excretion does not cause clinical problems. Xanthine, on the other hand, is less soluble than uric acid. Precipitated xanthine can be found in the urine of patients receiving allopurinol, but these precipitates do not correlate with the development of renal failure.[109] However, well-documented cases of xanthine nephropathy and xanthine calculi associated with allopurinol use have been reported.[109,110]

The half-life of allopurinol is less than 2 hours owing to prompt renal elimination and rapid conversion to its chief metabolite, oxypurinol. Oxypurinol is an active metabolite and reduces serum uric acid concentration and urinary uric acid excretion half as much as allopurinol.[111] Unlike allopurinol, oxypurinol is eliminated solely by the kidney, with a half-life of approximately 24 hours.[111] Renal clearance of oxypurinol is decreased with reduced renal function and with creatinine clearance such that with a creatinine clearance of less than 10 mL per minute, the half-life of oxypurinol is approximately 1 week.

In patients with normal renal function and hyperuricemia associated with malignancy, allopurinol decreases serum uric acid within 48 hours with a peak effect at 5 days.[112] The clinical effects of allopurinol probably are mediated by oxypurinol because the half-life of allopurinol is short. Despite the use of allopurinol, hyperuricemia and acute uric acid nephropathy sometimes cannot be avoided, and reasons for this failure include a large tumor burden, aggressive chemotherapy, and the inability to delay chemotherapy until allopurinol has decreased the serum uric acid concentration.

For optimal prophylaxis, allopurinol should be administered at least 3 days before chemotherapy. The level of existing renal function also must be considered when dosing the drug. Allopurinol can lead to a life-threatening toxicity syndrome that is characterized by a diffuse, desquamative skin rash; fever; hepatic dysfunction; eosinophilia; and worsening renal function of unknown etiology, which, however, is consistent with a diffuse vasculitis. Eighty percent of patients reported with this toxicity had renal insufficiency.[113] Improper dosing of allopurinol also can lead to xanthine nephropathy.[113]

Optimal allopurinol dosing is reflected by a therapeutic serum oxypurinol concentration that ranges from 30 to 100 μmol per liter.[114] Patients with end-stage renal disease achieve therapeutic levels of oxypurinol after one dose of allopurinol (300 to 600 mg) and maintain this level until the next dialysis, at which time the serum level is reduced by 40%.[113] Therefore, the maintenance dose must be reduced in patients with renal insufficiency to avoid an accumulation of oxypurinol. The oral route is equivalent to intravenous dosing of allopurinol; therefore, intravenous dosing should be considered only in patients unable to take anything by mouth. A rectal administration of allopurinol is not effective and should not be used.[114] Allopurinol started at 300 to 600 mg is safe and achieves therapeutic levels of oxypurinol, but the peak clinical effect on uric acid production is not seen for 3 days.

Rasburicase. As previously mentioned, most mammals degrade purines to the soluble end product allantoin, using the enzyme uricase (Fig. 36.2), which humans lack. Rasburicase, the recombinant form of urate oxidase, has several advantages over allopurinol. Rasburicase has a rapid onset of action and has been shown to return uric acid to normal levels with hours.[115,116] Unlike allopurinol, which inhibits the production of uric acid, rasburicase quickly reduces the existing uric acid levels and does not rely on the renal clearance of existing uric acid or alkalization of the urine. In one compassionate use trial, rasburicase (0.20 mg per kilogram) was administered intravenously once a day for 1 to 7 days. The mean uric acid level in 29 hyperuricemic children decreased from 15.1 to 0.4 mg per deciliter, and in 27 hyperuricemic adults, the mean level decreased from 14.2 to 0.5 mg per deciliter.[117] Rasburicase is an expensive drug and although clinical trials have compared rasburicase to allopurinol, the outcomes have been a decrement in uric acid levels rather than important metabolic outcomes or AKI.[115,116] Furthermore, there are recent reports of methemoglobinemia and hemolytic anemia that may be related to the use of rasburicase.

Forced Diuresis. Animal data have suggested that high renal tubular fluid flow induced by a solute or water diuresis is important in the prevention of acute urate nephropathy. In fact, rats treated with high-dose furosemide and Brattleboro rats with central diabetes insipidus and water diuresis both had complete protection from uric acid nephropathy, whereas rats treated solely with urine alkalinization had only partial protection.[118] Diuresis probably imparts protection by lowering the urate concentration in the collecting duct where uric acid precipitation occurs, or by effects on tubular urate handling. Whether these results can be applied to humans is not known because species differences in urate handling exist.

Despite efforts to maintain high urine flow with hydration and diuretics, a lower urine flow rate preceding chemotherapy is more common in patients who have renal failure than in those who do not.[102] Although this observation probably reflects the existence of mild spontaneous uric acid nephropathy before chemotherapy, it is reasonable to assume that increased urine flow would add protection from uric acid nephropathy. Patients should be hydrated with 4 to 5 L of normal saline every 24 hours. If the patient is well hydrated and not maintaining the expected urine output, diuretics should then be initiated. If urine output remains

low, fluid intake should be adjusted to match output in the effort to avoid fluid overload.

Urinary Alkalinization. Although evidence is lacking to confirm its role in preventing uric acid nephropathy, urinary alkalization remains a prominent component in prophylactic regimens. The theoretical benefit of urinary alkalinization is to increase the solubility of uric acid. However, in animal studies, the most important intrarenal dynamic in the prevention of acute uric acid nephropathy was high urine tubular flow.[118] In this study, the use of acetazolamide achieved only partial protection, which was likely due to the drug's diuretic effect and not its effect on urine pH.[118] Along with the inherent risk of causing a severe metabolic alkalosis when attempting to alkalinize the urine with sodium bicarbonate administration, other potential disadvantages include increasing the risk of symptomatic hypocalcemia and calcium phosphate precipitation, which can cause AKI by itself in this setting.[119] Urinary alkalinization also does not have an effect on xanthine precipitation because the pK_a of xanthine is 7.4, as opposed to 5.6 for uric acid.

Bicarbonate therapy should be included in the prophylactic regimen only when attempting to correct hyperuricemia. If hyperuricemia is present before chemotherapy, bicarbonate should be added to intravenous fluids with the aim of keeping the urine pH above 7.0. Once hyperuricemia has been corrected, bicarbonate therapy should be discontinued.

Hemodialysis. Dialysis assists in the management of acute uric acid nephropathy in two ways. First, dialytic therapy is initiated for the typical indications common in AKI such as hyperkalemia, severe hyperphosphatemia, azotemia, and fluid overload, although these indications may be more severe and may occur more rapidly than in other forms of AKI. Cases of fatal hyperkalemia have occurred within hours after the initiation of chemotherapy.[119] Second, dialysis is an effective way to reduce the serum uric acid level. This is an important role for dialysis because patients usually do not recover from acute uric acid nephropathy until the serum uric acid level is reduced.[120] Once this occurs, usually after only one to four dialysis treatments, recovery of renal function is signaled by a brisk diuresis.

Depending on the dialyzer and blood flow used, hemodialysis has a uric acid clearance rate of 90 to 150 mL per minute, whereas peritoneal dialysis clearance is only 10 to 20 mL per minute.[120,121] When starting a patient on hemodialysis, caution should be taken not to use a high-calcium bath if severe hyperphosphatemia is present because of the risk of increasing the calcium–phosphorus product. Selected patients may benefit from continuous renal replacement therapy such as CVVHD.

Ethylene Glycol Toxicity

Acute ethylene glycol intoxication is a medical emergency that, if not treated aggressively, leads to serious neurologic, cardiopulmonary, and renal dysfunction, and may result in death. Ethylene glycol, an odorless and clear liquid, is the major ingredient in antifreeze, and is most commonly consumed either intentionally by alcoholics seeking an ethanol substitute or accidentally by children. An ingestion of 100 mL is considered the minimal lethal dose of ethylene glycol.[122,123] Diethylene glycol is a condensation product of ethylene glycol production, and ingestion causes the same toxicities as ethylene glycol.[124] Diethylene glycol was used as the diluent in the first sulfa antibiotic, sulfanilamide, and consequently led to mass poisonings in 1937. One hundred five patients died from the therapeutic use of Elixir Sulfanilamide, and one important consequence of this tragedy was the 1938 Federal Food Drug and Cosmetic Act requiring proof of product safety before release of a drug.[125] Unfortunately, this kind of governmental supervision of pharmaceutical companies does not exist in other countries such as Nigeria and Haiti, where 47 and 85 children, respectively, died when diethylene glycol was used as a solvent in a preparation of cough syrup.[126,127]

Metabolism of Ethylene Glycol

The metabolism of ethylene glycol is complex and incompletely understood. As is the case with other alcohols such as ethyl and methyl alcohol, nicotinamide adenine dinucleotide (NAD)-dependent alcohol dehydrogenase is responsible for the first oxidative step converting ethylene glycol to glycolaldehyde (Fig. 36.5). After this first step the pathways have not been well elucidated in humans, but are thought to include the following: glycolaldehyde oxidized to glycolic acid by aldehyde oxidase, glycolic acid to glyoxylate by glycolic acid oxidase or LDH, and then numerous subsequent pathways for glyoxylate metabolism, including one to oxalate by LDH and glycolic acid oxidase (Fig. 36.5).[122] Glycolate is converted to glyoxylate very slowly and is probably the rate-limiting step in the metabolism of ethylene glycol, whereas glycolaldehyde and glyoxylate have very short half-lives.[128]

Ethylene glycol metabolites are thought to mediate the toxicity seen with ethylene glycol ingestion, and ethylene glycol itself is not toxic. In fact, the inhibition of ethylene glycol metabolism with ethyl alcohol or pyrazole prevents toxicity.[129,130] The observation that the mortality rate in rats is reduced by performing a partial hepatectomy before the administration of ethylene glycol and glycolate illustrates the importance of ethylene glycol metabolites on toxicity. The partially hepatectomized rats metabolized ethylene glycol more slowly to its toxic byproducts, which allowed more time for renal excretion of the nontoxic and unchanged ethylene glycol.[131] Glycolate and oxalate are thought to be important mediators of ethylene glycol toxicity.

The pathophysiologic process of ethylene glycol toxicity is multifactorial and is thought to include the accumulation of toxic ethylene glycol metabolites, calcium oxalate crystal deposition in tissues, and the effects of severe acidosis. After the administration of a lethal dose of ethylene glycol in rats, profound renal oxalosis is produced, and the same occurs with administration of glycolic acid and glyoxylic acid. Renal

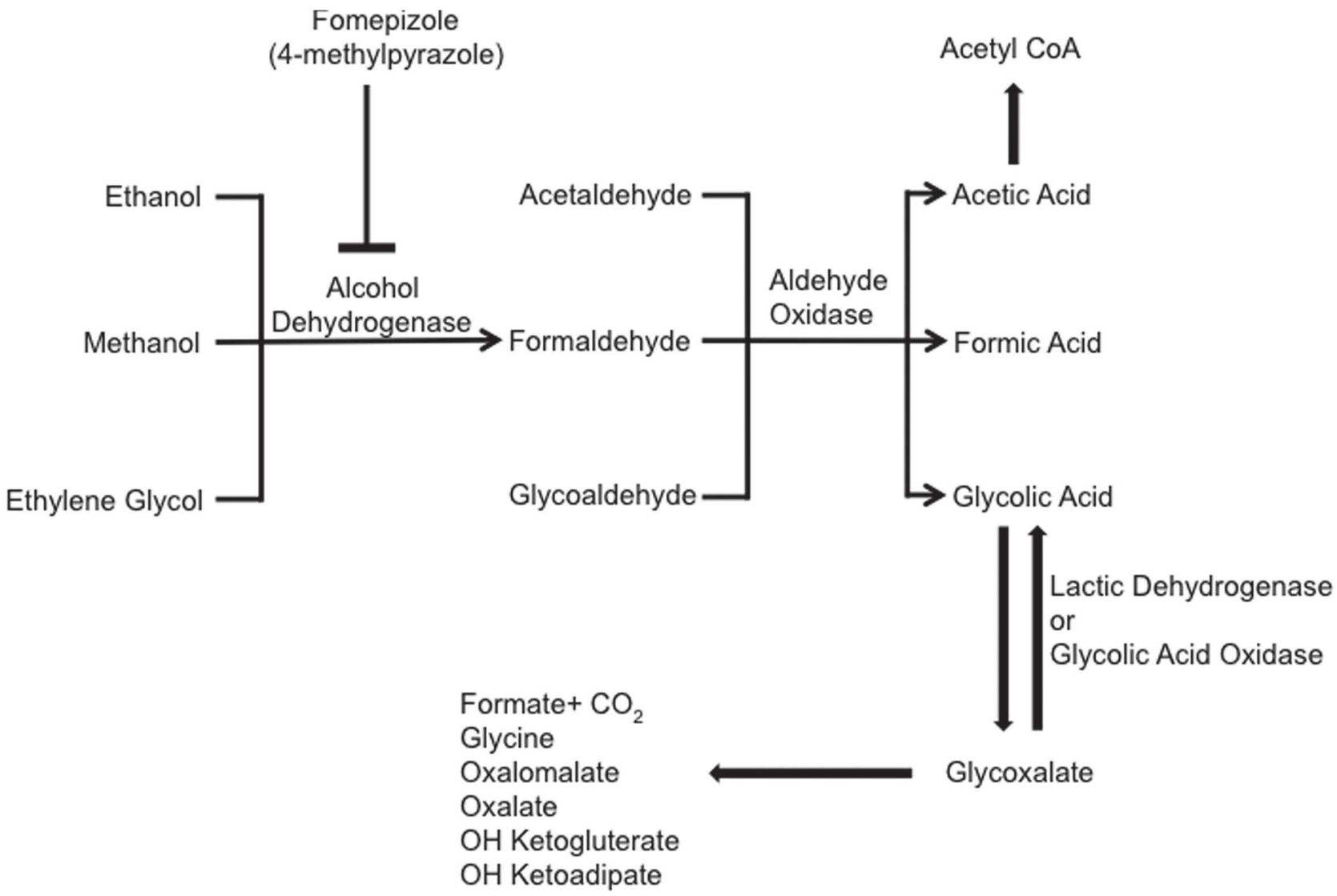

FIGURE 36.5 The pathway of ethylene glycol degradation.

pathology in these rats demonstrated calcium oxalate crystals in the proximal and distal convoluted tubules, with smaller amounts in the collecting tubule and none in the glomeruli or renal interstitium.[132] The degree of crystal formation correlated with diffuse convoluted tubular dilatation, but occasional epithelial necrosis seemed to bear a relation to the degree of crystal formation. The administration of glycolaldehyde did not produce significant crystal formation or the same degree of microscopic changes, but did lead to pronounced tubular epithelial swelling. In addition to the renal findings, oxalate crystals were found in brain tissue.[132] In dogs given nonlethal doses of ethylene glycol, renal biopsy specimens revealed interstitial edema, tubular dilatation, hydropic degeneration, and tubular cell necrosis even in areas free of crystals. Electron microscopic findings were most prominent in proximal tubule cells and included vacuolization, cellular rupture, cytoplasmic buds, and increased density of mitochondria.[133] This pattern of proximal tubule damage is similar to other models of ischemic and nephrotoxic forms of AKI.[133]

These findings are similar to human autopsy series that also have found calcium oxalate crystals in renal tubules. In these studies, renal epithelial cells appear either normal or extensively necrotic depending on the interval between ingestion and death and appear minimal if any damage of the glomeruli has been reported.[122,123] Despite severe clinical neurologic disturbances, the brain characteristically has only mild perivascular and meningeal deposition of calcium oxalate crystals, but edema, capillary engorgement, hemorrhage, and infarctions also have been described.[122,123,134] Although crystal deposition usually is not reported, myocardial tissue findings are consistent with myocarditis.[134] Autopsy and renal biopsy studies do not support the hypothesis that calcium oxalate crystallization is the primary cause of ethylene glycol toxicity; despite widespread renal tubule damage, calcium oxalate crystal deposition is patchy; and despite the presence of crystals there is no tubule obstruction or dilatation.

High–anion-gap metabolic acidosis is a major feature of ethylene glycol intoxication, and is also thought to contribute directly to the clinical toxicity. In rats poisoned with ethylene glycol, survival rates are five times greater after treatment with sodium bicarbonate alone or with ethanol alone compared with no treatment. Giving ethanol and sodium bicarbonate together improved the survival rate to six times that seen in rats with no treatment.[135] The major determinant of the metabolic acidosis is glycolic acid; in dogs and monkeys, the administration of ethylene glycol produces severe metabolic acidosis and the depressed bicarbonate is matched by the increase in glycolic acid production.[122] Oxalic acid is very toxic to kidneys and is lethal in doses much lower than toxic doses of ethylene glycol, but in rats and monkeys, only 0% to 2.5% of the original dose of ethylene glycol is excreted as oxalic acid.[136,137] In humans with ethylene glycol poisoning, the plasma glycolate concentration correlated with the increased anion gap, and the serum concentrations of oxalate and glyoxylate were negligible in these patients.[122,128] Although studies have suggested that organic acids such as lactic acid contribute to the severe metabolic acidosis of ethylene glycol intoxication, glycolic acid seems to be the main cause of the acidosis with lactic and β-hydroxybutyric acids being elevated in special circumstances such as that associated with hypotension or alcoholic ketoacidosis.[138,139]

It has been postulated that the production of glycolaldehyde, glyoxal, glycolate, and glyoxylate from ethylene glycol metabolism is important in the pathophysiologic process of toxicity. Aldehyde production is greatest 6 to 12 hours after ethylene glycol ingestion, and this is when cerebral symptoms are most severe.[122,123] However, as mentioned, glycolate is the only metabolite that accumulates; its direct toxicity has not been well studied, but it is known to be toxic in animals.[137] For example, glycolic acid given to rats is lethal and also causes renal tubular oxalosis.[132] The role that glycolic acid plays in human renal, cerebral, and cardiac toxicity remains to be proven, but it probably is one of the multifactorial causes along with acidosis and calcium oxalate crystals.

Clinical and Laboratory Manifestations

The initial reports of ethylene glycol poisoning in the 1940s and 1950s noted that the clinical manifestations of acute ethylene glycol poisoning could be divided into three stages.[140] During the first stage, occurring 30 minutes to 12 hours after ethylene glycol ingestion, the central nervous system manifestations predominate. During the second stage, occurring over the next 12 hours, cardiopulmonary dysfunction develops and includes tachypnea, pulmonary edema, and cardiac failure. In patients who survive past the first 24 hours, the third stage is characterized by prolonged renal failure. Before the advent of aggressive treatment with hemodialysis and intravenous ethanol, these stages were very typical of the clinical course of most patients, but with modern treatment and depending on the amount of ethylene glycol ingested, the sequence and occurrence of these clinical features and stages vary considerably.[122,123]

In addition to apparent inebriation without an alcoholic odor, central nervous system manifestations include nystagmus, depressed reflexes, seizures, and coma.[122,123] The delayed appearance of multiple cranial nerve deficits also has been reported, and the deficits have not always been reversible.[141] Ocular effects are a main feature of methanol ingestion but ophthalmoplegia, papilledema, loss of visual acuity, and eventual optic atrophy also have been reported with ethylene glycol ingestion.[142] Abdominal signs and symptoms including nausea, vomiting, and pain are very common.[122,123] For unexplained reasons, mild hypertension, tachycardia, and a low-grade fever sometimes are present.[122,123]

High–anion-gap metabolic acidosis with a high osmolar gap is the most striking initial laboratory finding and, when combined with clues in the history of the patient, is the main diagnostic feature. The severity of the clinical presentation depends on the quantity of ingested ethylene glycol and the elapsed time since its ingestion, but typically, patients present with a pH of less than 7.2, bicarbonate less than 10 mEq per liter, anion gap greater than 20, mean osmolal gap of 35, measured osmolality greater than 300 mOsm, and hyperkalemia.[122,123] Hypocalcemia is a frequent finding and can be severe and symptomatic leading to tetany or cardiac arrhythmia.[122,123] The onset of hypocalcemia is usually within the first 12 hours, and serum calcium usually remains low despite treatment. Hypocalcemia probably is caused by a combination of chelation of calcium by oxalate and an abnormal parathyroid hormone response.[122,123]

Lumbar puncture frequently is performed because of mental status changes, and the cerebrospinal fluid sometimes reveals pleocytosis with a sterile culture.[122,123,134] A normal hematocrit and platelet count, but a moderate leukocytosis of 10,000 to 40,000/mm^3 with a predominance of polymorphonuclear cells is seen commonly in the initial complete blood count.[122,123,134]

The urinalysis typically includes a low specific gravity, mild proteinuria, microscopic hematuria, and pyuria.[122,123] Crystalluria is not invariably present but usually is seen on presentation. The envelope-shaped calcium oxalate dihydrate form of crystal (octahedral dihydrate) (Fig. 36.4C) traditionally has been thought of as the most commonly seen crystal in ethylene glycol intoxication, but in fact needle-shaped monohydrate calcium oxalate crystals predominate in ethylene glycol intoxication.[122,123] Monohydrate calcium oxalate crystals are thermodynamically stable, and with time, the dihydrate form transforms to the monohydrate form.[143] In vitro, the dihydrate form is seen only at high concentrations of both calcium and oxalate.[143] The pattern of oxalate crystals in individual patients transforms from the envelope-shaped crystals to the needle-shaped crystals in a matter of hours.[138]

The cardiopulmonary consequences of ethylene glycol intoxication now are rarely seen with prompt, aggressive treatment. After the ingestion of ethylene glycol sufficient to cause metabolic acidosis, oliguric renal failure develops in most patients.[144,145] If aggressive treatment, including dialysis and fomepizole or ethanol, is provided soon after the ethylene glycol is ingested, renal failure can be avoided. However, most patients do not seek medical attention until symptoms develop, which usually is many hours after ingestion. Thus, renal failure is common and may develop as soon as 24 hours after ingestion.[122,146] The course of the renal failure is typical of oliguric acute tubular necrosis. The oliguria lasts 4 to 5 days and is followed by a diuretic phase. BUN and serum creatinine usually peak at 7 to 10 days, and most patients require only 1 to 2 weeks of dialytic support.[147,148] However, some patients require dialysis for many months, and despite the return of sufficient kidney function to stop dialysis, kidney function does not always return to baseline values.[138]

Diagnosis

In the absence of ketoacidosis, and in the presence of the characteristic signs and symptoms, it should be assumed that all patients presenting with metabolic acidosis combined with increased anion and osmolal gaps have either methanol or ethylene glycol poisoning.[148] The prognosis of both these poisonings is improved with early diagnosis and treatment, and therefore, if the diagnosis cannot be confirmed with serum levels of methanol or ethylene glycol treatment with

bicarbonate and ethanol infusion and hemodialysis should be initiated.[148] Determining specific levels of each alcohol is the most specific test. Because these tests are not available in all hospitals,[149] adding fluorescein to the urine and then observing for urine fluorescence with an ultraviolet Wood lamp is helpful in making the diagnosis.

Once the diagnosis of ethylene glycol poisoning has been confirmed and the blood concentration of any concomitantly ingested ethanol has been determined, the serum ethylene glycol level can be estimated using the osmolal gap.[150,151] Ethylene glycol levels above 20 mg per deciliter can be lethal if not treated aggressively.[144]

Clinical Course and Treatment

Initial Emergency Department Treatment. Gastric lavage should be initiated to reduce further drug absorption if the patient is seen in the first few hours after ethylene glycol ingestion.[148,152] Both methanol and ethylene glycol intoxication were previously treated with an ethanol infusion (to prevent the production of toxic metabolites) followed by hemodialysis to remove the actual substance from the body.[148,152] However, fomepizole (4-methylpyrazole; Antizol) is now the drug of choice.[153,154] Hemodialysis to provide a source of bicarbonate and to clear ethylene glycol and its metabolites is the therapy of choice for the treatment of the acidosis. However, hemodialysis usually is delayed and during this waiting period, patients require large doses (300 to 500 mEq) of sodium bicarbonate, and the metabolic acidosis is not corrected until hemodialysis is initiated.[155]

Correction of the acidosis may increase the likelihood of symptomatic hypocalcemia such as seizures, tetany, and cardiac dysfunction. Intravenous calcium supplementation should be given cautiously because of the potential risk of further calcium oxalate precipitation. Calcium should be given if clinical signs or symptoms of hypocalcemia develop, but not prophylactically.[148,152] Thiamine and pyridoxine are cofactors required in the nontoxic metabolic pathways of ethylene glycol (away from oxalate), and early replacement of these cofactors is advocated to prevent potential depletion.[148,152]

The administration of ethanol and hemodialysis has traditionally made up the definitive treatments for ethylene glycol intoxication. Compared with ethylene glycol, ethanol has a higher affinity for alcohol dehydrogenase and therefore inhibits the metabolism of ethylene glycol to the toxic metabolites, permitting the ethylene glycol to be renally excreted or dialyzed. With a blood ethanol level of 100 mg per deciliter liver alcohol dehydrogenase is saturated, and the half-life of ethylene glycol increases from 3 to 17 hours.[122,148,152] Since the first report of ethanol treatment in humans, ethanol has been used in conjunction with dialysis in the treatment of ethylene glycol poisoning, and ethanol is not recommended as a sole treatment.[129] Although there have been reports of successful treatment with ethanol without dialysis, these were isolated cases in which ingestion only of small amounts of ethylene glycol occurred.[156]

For the maximal inhibition of ethylene glycol metabolism, the plasma ethanol concentration should be maintained between 100 and 200 mg per deciliter. This is achieved with a loading dose of 0.6 g per kilogram, followed by a maintenance dose of 66 mg per kilogram in nondrinkers, and 154 mg per kilogram in regular alcohol consumers. During dialysis, 7.2 g per hour should be added to the maintenance dose.[157] Oral ethanol also can be used, but the dose should be increased by 50% if given soon after the administration of charcoal.[157] Intravenous ethanol comes in 5% and 10% solutions diluted in dextrose and water, whereas a 20% or 50% solution usually is used for oral or nasogastric administration. The specific gravity of ethanol is used in calculating the correct dose.[157] Until the correct dose to achieve a level between 100 and 200 mg per deciliter has been ascertained, hourly ethanol concentrations should be checked. The dosing guidelines for ethanol in ethylene glycol toxicity is summarized in Table 36.8.

36.8 Dosing Guidelines for Ethanol Treatment

Ethanol Solution and Route of Administration	Specific Gravity of Ethanol (g/dL)	Loading Dose (100 mg/dL of ethanol × 0.6 L/kg) (mL/kg)	Maintenance Dose in Nondrinkers 66 mg/kg/hr (mL/kg/hr)	Maintenance Dose in Drinkers 154 mg/kg/hr (mL/kg/hr)	During Dialysis Add the Following to the Maintenance Dose (mL/hr)
5% IV	3.9	15.4	1.7	3.9	185
10% IV	7.8	7.7	0.84	2.0	90
20% PO	15.8	3.8	0.42	1.0	45
50% PO	39.5	1.5	0.17	0.4	18

Oral ethanol dose should be increased by 50% after charcoal therapy. IV, intravenous; PO, orally.

4-Methylpyrazole (Fomepizole). Fomepizole is a potent inhibitor of alcohol dehydrogenase, and animal studies have shown that fomepizole prevents ethylene glycol–related mortality and toxicities, and increases the urinary excretion of ethylene glycol by preventing its metabolism.[130] In humans, fomepizole has been shown to normalize acidosis within hours, to prevent decreases in renal function if used early, and to decrease serum levels of ethylene glycol toxic metabolites.[153,154,158] In humans without AKI, treatment results in an increase in the ethylene glycol half-life from 3 to 14 hours, an increase in urinary excretion of ethylene glycol, and the prevention of clinical toxicity.[153,154]

Fomepizole offers advantages over ethanol treatment including predictable pharmacokinetics, avoiding the need to achieve and maintain the desired blood ethanol level, and avoiding an ethanol-induced central nervous system depression. Fomepizole is available as a parenteral solution. The loading dose is 15 mg per kilogram intravenously, followed by 4 more doses of 10 mg per kilogram every 12 hours, after which it is continued at a rate of 15 mg per kilogram every 12 hours until the ethylene glycol concentration is undetectable or the patient is asymptomatic with a resolution of the high–anion-gap metabolic acidosis. Like ethanol, the dose of fomepizole is adjusted during dialysis therapy. At the start of dialysis, the next scheduled dose is given if it has been longer than 6 hours since the last dose, but if it has been less than 6 hours, the next scheduled dose is held. Fomepizole is then given every 4 hours during dialysis. At the completion of dialysis, no additional dose is given if it has been less than 1 hour since the last dose, one-half of the next scheduled dose is given if it has been 1 to 3 hours since the last dose, and the next scheduled dose is given if it has been longer than 3 hours since the last dose. The maintenance dose off dialysis is continued 12 hours after the last dose.[153,154]

Fomepizole has been used to treat ethylene glycol poisoning successfully without hemodialysis or ethanol, but these patients had normal renal function, and fomepizole treatment was initiated soon after ethylene glycol ingestion.[159,160] In mild cases of ethylene glycol poisoning, as evidenced by normal renal function and no high–anion-gap acidosis, ethanol or fomepizole is used by some as sole therapy without dialysis. However, in these cases, forced diuresis with intravenous fluids or furosemide should be used to avoid dehydration, minimize renal calcium oxalate crystal formation, and maintain the renal clearance of ethylene glycol.[159] More recent data suggest that an abnormal presenting serum creatinine concentration ($\geq$1.5 mg per deciliter) predicts significantly prolonged ethylene glycol elimination during fomepizole therapy, and in the presence of metabolic acidosis, patients should undergo hemodialysis.[161]

Hemodialysis. Hemodialysis is indicated in all cases of confirmed or strongly suspected ethylene glycol poisoning presenting with renal failure, metabolic acidosis, and/or deteriorating clinical status. Ethylene glycol and glycolate have low molecular weights, no protein binding, and a volume of distribution of 0.8 and 0.55 L per kilogram, respectively, making them easily dialyzable.[147,148,152] Large surface-area dialyzers ($>$2 m^2) can achieve a clearance of ethylene glycol of greater than 200 mL per minute, and with smaller surface-area dialyzers (1.1 to 1.6 m^2) clearance of ethylene glycol and glycolate typically ranges from 150 to 190 mL per minute and 140 to 170 mL per minute, respectively.[147,148,152] The renal clearance of ethylene glycol can be as high as 30 mL per minute in patients with preserved renal function, but the importance of hemodialysis is illustrated by the fact that most patients present with renal insufficiency, and in these patients the renal clearance of ethylene glycol and glycolate is negligible.[162] The length of the hemodialysis session should be determined by the quantity of ethylene glycol ingested, but this rarely is known. Although blood ethylene glycol levels are helpful, they do not necessarily reflect the total quantity ingested because the blood ethylene glycol level is influenced by time since ingestion and amount metabolized. Dialysis should be continued for 8 hours if ethylene glycol levels are not available, and when levels are available, the dialysis prescription should be calculated using the total body water, the blood ethylene glycol level, and the manufacturer-specified dialyzer urea clearance (in milliliters per minute) at the initial observed blood flow rate.[163] Bicarbonate-based dialysate is probably optimal compared with acetate dialysate, which is associated with greater hemodynamic instability, more central nervous system symptoms, and more oscillations in plasma bicarbonate.[164] Although peritoneal dialysis clears ethylene glycol and oxalate, it should not be used over hemodialysis because of the high efficacy of hemodialysis.[165]

Sulfonamide Antibiotics, Indinavir, and Acyclovir

Crystal-induced AKI also can be caused by drugs used for therapeutic purposes. If the solubility limit of a given drug is exceeded in the renal tubules, the drug can then crystallize and possibly cause obstructive nephropathy. Certain sulfonamide antibiotics and acyclovir are the most common drugs that can cause crystalline AKI, but other drugs such as methotrexate, triamterene, acetazolamide, several herbal medicines, and high-dose vitamin C potentially can crystallize and cause stones or obstructive nephropathy.[166–169] Before the AIDS era, crystalline AKI had become fairly rare, but with the frequent use of high-dose sulfadiazine, sulfamethoxazole, indinavir, tenofovir, and acyclovir in this population, it is again an important cause of AKI.[170,171]

Sulfonamides. The sulfonamides were introduced into medical practice in 1936, and early animal experiments recognized that sulfonamides of low solubility were able to crystallize in the urinary tract and the renal parenchyma, causing obstructive nephropathy.[172,173] Reports of patients with hematuria, crystalluria, renal colic, and renal failure were common until the 1950s, when sulfonamides with greater solubility became available.[172] In patients with AIDS, high-dose sulfadiazine is again commonly being used in

conjunction with pyrimethamine for the treatment of toxoplasmosis. After an oral dose, sulfadiazine is rapidly absorbed and then partially acetylated in the liver. The half-life of sulfadiazine is 8 to 17 hours in patients with normal renal function and is 22 to 34 hours in patients with severe renal insufficiency.[171] Renal crystal formation in the nephron is promoted as the filtrate is concentrated and acidified. The solubility of sulfadiazine is almost 10-fold higher at a pH of 7.5 than at a pH of 6.5.

Patients with sulfonamide-induced AKI classically present with renal colic, hematuria, and oliguria or anuria.[174] Although renal failure develops in most patients in the first week after the start of the sulfadiazine patients also can present months after the start of the medication. Delayed presentation of AKI usually occurs with the concurrent development of volume depletion, often due to diarrhea, and these patients can be managed with hydration without stopping the sulfadiazine.[175] The urinalysis usually shows hematuria, mild pyuria, and "shock of wheat" crystals (Fig. 36.4D). Renal ultrasonography may reveal multiple echogenic foci in the renal parenchyma, but occasionally may show frank hydronephrosis with ureteral stones.[175,176]

AKI should be managed with intravenous fluids containing sodium bicarbonate with the aim of maintaining urine pH over 7.15 and urine output over 1 L per day. Urologic intervention sometimes is required in patients who remain anuric. Bilateral retrograde ureteral catheterization with warm 5% sodium bicarbonate solution, ureteral stents, and stone extraction with a stone basket all have been used in cases of ureteral obstruction with stones.[177] Although temporary hemodialysis sometimes is necessary, the recovery of renal function to baseline is the rule within 7 days.[176]

Patients starting sulfadiazine therapy should receive prophylaxis against renal toxicity. To minimize crystal formation, patients should be encouraged to maintain fluid intake over 2 to 3 L per day and should be started on sodium bicarbonate (6 to 12 g per day) to maintain a urine pH higher than 7.15.[174] Patients with renal insufficiency, diarrhea, or volume depletion should be monitored closely with urinalyses looking for hematuria and crystalluria, and sulfadiazine levels should be considered in patients with renal insufficiency.[174]

Indinavir. Indinavir is one of the most common protease inhibitors used in patients with AIDS as part of a highly active antiretroviral therapy. Indinavir causes nephrolithiasis in 3% to 4% of patients, and symptomatic urinary tract disease, including nephrolithiasis with renal colic, flank pain without evidence of stones, and dysuria or urgency in 8% of patients taking the drug.[178,179] Most patients presenting with symptomatic urinary tract disease have crystalluria, and many have radiographic evidence of either stones or renal parenchyma filling defects. However, only a minority of patients have mild-to-moderate renal insufficiency. Hydration can prevent symptomatic urinary tract disease, but a permanent discontinuation of indinavir is necessary in some because of recurrence of symptoms. Asymptomatic indinavir crystalluria is found in 20% of patients receiving the drug in the normal dosage of 800 mg orally three times a day, and the drug should not be discontinued for asymptomatic crystalluria. The presence of crystalluria and pyuria may signal the presence of interstitial nephritis, which may not reverse with conservative treatment with hydration alone.[180]

Acyclovir. High-dose acyclovir also is associated with AKI and crystalluria. Early preclinical toxicology studies in animals clearly demonstrated that high-dose acyclovir given to rats resulted in the precipitation of drug crystals in the distal nephron and also caused reversible obstructive nephropathy.[181,182] Although it has been assumed that intratubular acyclovir crystallization is also responsible for the renal failure observed in humans, the pathophysiologic process is not entirely clear. Most reported kidney biopsy or autopsy specimens have not demonstrated intrarenal crystals, but typically show normal glomeruli, no obstruction, occasional ruptured tubules, and minimal focal areas of interstitial hemorrhage, congestion, and inflammatory infiltrates.[183,184] In one case report of acyclovir nephrotoxicity, the renal biopsy was consistent with acute tubular necrosis without any evidence of intratubular crystals.[185] Crystal dissolution during tissue fixation or the time interval between discontinuation of acyclovir and obtaining the renal biopsy could account for the inconsistent demonstration of crystals in renal tissue.[185]

Renal impairment after intravenous acyclovir was commonly observed when bolus injections were used instead of slow infusions; one series reported that increased BUN or serum creatinine levels developed in 58 of 354 (16%) of patients 24 to 48 hours after the administration of acyclovir.[182,186] Unlike all other subsequent reports, one infant in this series with renal failure did show birefringent crystals in the renal tubules at the postmortem examination.[182] In contrast to bolus injections, renal failure after slow intravenous infusions or oral acyclovir is less common but does occur, especially in patients with renal insufficiency or volume depletion.[184]

AKI caused by acyclovir typically develops 24 to 72 hours after the first dose of intravenous acyclovir. Unlike with the sulfonamide antibiotics, most patients do not have renal colic, stones, or ultrasonographic findings of obstruction. Many patients also have neurotoxicity, including headache, irritability, tremulousness, ataxia, nystagmus, lethargy, dysarthria, confusion, and coma.[184] The urinalysis usually reveals both mild hematuria and pyuria, and an examination of the urine with a polarizing microscope may show birefringent, needle-shaped crystals within leukocytes.[184,187]

Risk factors for the development of acyclovir-induced AKI include volume depletion, bolus dosing, chronic renal failure, and an acyclovir serum level of greater than 25 μg per milliliter.[182,188] The renal function in patients with AKI usually normalizes within 4 to 9 days after drug discontinuation.[184,188] Conservative management, with hydration and the discontinuation of acyclovir, is sufficient in most

patients, but in patients with combined severe neurotoxicity and nephrotoxicity, hemodialysis can be used to reduce serum acyclovir levels. This results in the prompt reversal of acyclovir-associated neurologic symptoms.[187] In cases of mild renal failure, acyclovir nephrotoxicity can be managed by hydration and dose reduction of acyclovir.[189]

The half-life of acyclovir is 3 hours, and renal excretion is the major route of elimination. For example, over 90% of a given dose of acyclovir can be recovered unchanged in the urine of subjects with normal renal function 12 hours after dosing.[190] There is a linear relationship between creatinine clearance and the renal clearance of acyclovir. The renal clearance of acyclovir is three times that of a given creatinine clearance, indicating significant tubular secretion.[190] In subjects with preexisting renal insufficiency, the half-life of acyclovir can be as high as 20 hours, and dosing in renal insufficiency should be adjusted according to the level of renal function.[190,191] Hemodialysis effectively removes acyclovir, reducing the half-life to 5 hours, and can effectively remove 40% of acyclovir in body stores.[190,192]

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