REVIEW ARTICLE

CURRENT CONCEPTS

Rhabdomyolysis and Acute Kidney Injury

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Rhabdomyolysis — literally, the dissolution of striped (skeletal) muscle — is characterized by the leakage of muscle-cell contents, including electrolytes, myoglobin, and other sarcoplasmic proteins (e.g., creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) into the circulation. Massive necrosis, which is manifested as limb weakness, myalgia, swelling, and, commonly, gross pigmenturia without hematuria, is the common denominator of both traumatic and nontraumatic rhabdomyolysis.[1,2] Acute kidney injury is a potential complication of severe rhabdomyolysis, regardless of whether the rhabdomyolysis is the result of trauma or some other cause, and the prognosis is substantially worse if renal failure develops. In contrast, in less severe forms of rhabdomyolysis or in cases of chronic or intermittent muscle destruction — a condition sometimes called hyperCKemia — patients usually present with few symptoms and no renal failure. We review the pathophysiological characteristics and management of acute kidney injury associated with rhabdomyolysis.

There are eight commonly reported categories of rhabdomyolysis (Table 1). Exogenous agents that can be toxic to muscles, especially alcohol, illicit drugs, and lipid-lowering agents, are common nontraumatic causes. Recurrent episodes of rhabdomyolysis are often a sign of an underlying defect in muscle metabolism.[1,3,4]

Acute rhabdomyolysis occasionally develops in patients with structural myopathies when they are performing strenuous exercise, are under anesthesia, have taken drugs that are toxic to muscles, or have viral infections.[1] When a diagnosis of acute rhabdomyolysis is suspected, histochemical, immunohistochemical, and mitochondrial respiration studies performed on a muscle-biopsy specimen may yield a specific diagnosis. It is important to wait several weeks or months after the clinical event to perform a biopsy, because the results of a biopsy will typically be uninformative at an early stage. Thus, the specimen may appear normal or show no specific findings other than necrosis during and early after the acute episode of rhabdomyolysis (Fig. 1).[2,5]

The mechanisms involved in the pathogenesis of rhabdomyolysis are direct sarcolemmic injury (e.g., trauma) or depletion of ATP within the myocyte, leading to an unregulated increase in intracellular calcium.[6,7] Sarcoplasmic calcium is strictly regulated by a series of pumps, channels, and exchangers that maintain low levels of calcium when the muscle is at rest and allow the increase that is necessary for actin–myosin binding and muscle contraction. Depletion of ATP impairs the function of these pumps, resulting in a persistent increase in sarcoplasmic calcium that leads to persistent contraction and energy depletion and the activation of calcium-dependent neutral proteases and phospholipases; the result is the eventual destruction of myofibrillar, cytoskeletal, and membrane proteins, followed by lysosomal digestion of fiber contents. Ultimately, the myofibrillar network breaks down, resulting in disintegration of the myocyte.[2] In the case of patients with rhabdomy-

Table 1. Major Categories and Commonly Reported Causes of Rhabdomyolysis.

Category	Commonly Reported Cause
Trauma	Crush syndrome
Exertion	Strenuous exercise, seizures, alcohol withdrawal syndrome
Muscle hypoxia	Limb compression by head or torso during prolonged immobilization or loss of consciousness,* major artery occlusion
Genetic defects	Disorders of glycolysis or glycogenolysis, including myophosphorylase (glycogenosis type V), phosphofructokinase (glycogenosis type VII), phosphorylase kinase (glycogenosis type VIII), phosphoglycerate kinase (glycogenosis type IX), phosphoglycerate mutase (glycogenosis type X), lactate dehydrogenase (glycogenosis type XI) Disorders of lipid metabolism, including carnitine palmitoyl transferase II, long-chain acyl-CoA dehydrogenase, short-chain L-3-hydroxyacyl-CoA dehydrogenase, medium-chain acyl-CoA dehydrogenase, very-long-chain acyl-CoA dehydrogenase, medium-chain 3-ketoacyl-CoA, thiolase† Mitochondrial disorders, including succinate dehydrogenase, cytochrome *c* oxidase, coenzyme Q10 Pentose phosphate pathway: glucose-6-phosphate dehydrogenase Purine nucleotide cycle: myoadenylate deaminase
Infections‡	Influenza A and B, coxsackievirus, Epstein–Barr virus, primary human immunodeficiency virus, legionella species *Streptococcus pyogenes, Staphylococcus aureus* (pyomyositis), clostridium
Body-temperature changes	Heat stroke, malignant hyperthermia, malignant neuroleptic syndrome, hypothermia
Metabolic and electrolyte disorders	Hypokalemia, hypophosphatemia, hypocalcemia, nonketotic hyperosmotic conditions, diabetic ketoacidosis
Drugs and toxins	Lipid-lowering drugs (fibrates, statins), alcohol, heroin, cocaine
Idiopathic (sometimes recurrent)	

* Rhabdomyolysis from this cause is associated with a crush syndrome–like mechanism.
† CoA denotes coenzyme A.
‡ In most cases, the mechanism is unclear.

olysis caused by trauma, additional injury results from ischemia reperfusion and inflammation by neutrophils that infiltrate damaged muscle.[8]

EPIDEMIOLOGY OF MYOGLOBINURIA-INDUCED ACUTE KIDNEY INJURY

Acute kidney injury associated with myoglobinuria is the most serious complication of both traumatic and nontraumatic rhabdomyolysis, and it may be life-threatening. Acute kidney injury as a complication of rhabdomyolysis is quite common, representing about 7 to 10% of all cases of acute kidney injury in the United States.[4,9] The true incidence of acute kidney injury in rhabdomyolysis is difficult to establish owing to varying definitions and clinical scenarios. The reported incidence ranges from 13% to approximately 50%.[9-11] In a study by Melli et al. involving 475 hospitalized patients with rhabdomyolysis, the incidence of acute kidney injury was 46%.[10] Although rhabdomyolysis from any cause can lead to acute kidney injury, in this study, the incidence of acute kidney injury was higher among persons who used illicit drugs or abused alcohol and among persons who had undergone trauma than among persons with muscle disease, and the incidence was particularly high among persons with more than one recognized causal factor.[10]

The outcome of rhabdomyolysis is usually good provided that there is no renal failure. Nevertheless, mortality data vary widely according to the study population and setting and the number and severity of coexisting conditions. In a study in which the incidence of vasculopathy leading to rhabdomyolysis as a result of limb ischemia was high, the overall mortality was 32%.[12] In contrast, the study by Melli et al. of hospitalized patients, in whom the abuse of illicit drugs and alcohol was the most frequently identified cause of rhabdomyolysis, showed a mortality of 3.4% among patients with acute kidney injury.[10] Among patients in the intensive care unit, the mortality has been reported to be 59% when acute kidney injury is present and 22% when it is not present.[13,14] Long-term survival among patients with rhabdomyolysis and acute kidney injury is reported to be close to 80%, and the majority of patients with rhabdomyolysis-induced acute kidney injury recover renal function.[14]

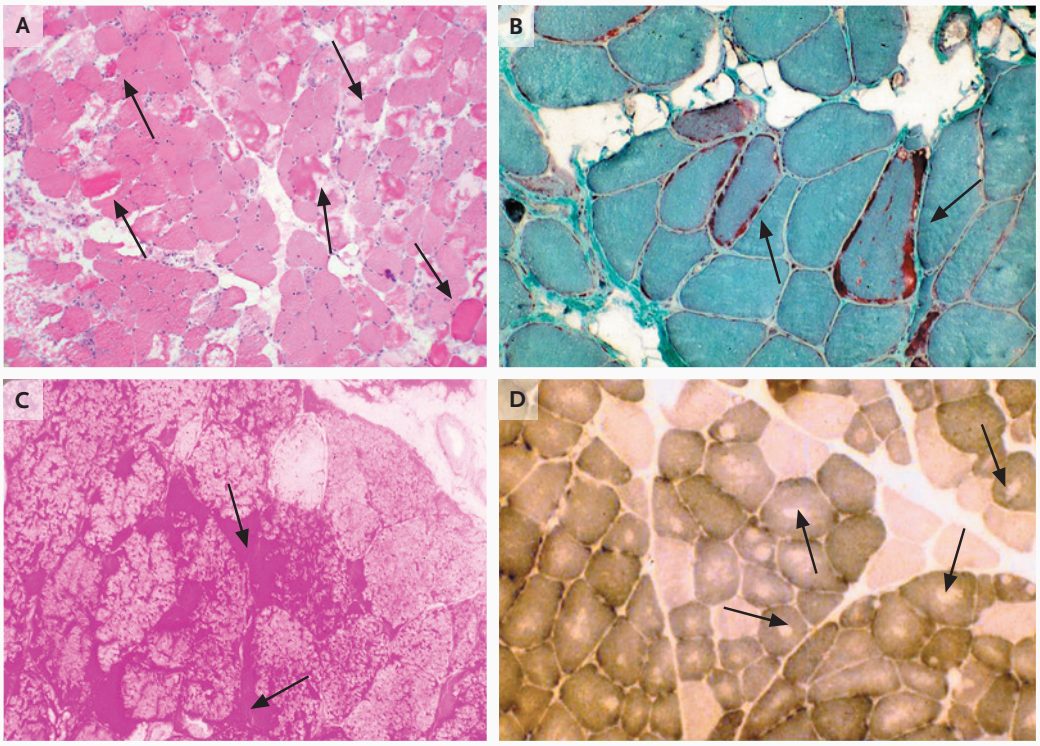


Figure 1. Histopathological Findings in Frozen Muscle-Tissue Specimens from Patients with Rhabdomyolysis.

Panel A shows massive muscle necrosis (arrows) in a patient with statin-related rhabdomyolysis (hematoxylin and eosin). This histologic feature would be similar in every case of rhabdomyolysis, irrespective of the cause. Panel B shows the typical ragged-red fibers (arrows) in a muscle-biopsy specimen from a patient with mitochondrial myopathy that was obtained 3 months after an episode of severe rhabdomyolysis. The mitochondrial dysfunction was confirmed by a mitochondrial respiratory chain–based assay (Gomori's trichrome). Panel C shows periodic acid–Schiff (PAS)–positive material (arrows) in some muscle fibers in a case of McArdle's disease. The biopsy was performed a few months after the patient's recovery from recurrent rhabdomyolysis (PAS stain). Panel D shows a muscle-biopsy specimen from a patient with central core disease. The specimen was obtained after the patient's recovery from malignant hyperthermia. Abundant central cores can be seen (arrows) (NADH–tetrazolium reductase stain).

PATHOGENESIS OF MYOGLOBIN-INDUCED ACUTE KIDNEY INJURY

Myoglobinuria occurs only in the context of rhabdomyolysis. Myoglobin is a dark red 17.8-kDa protein that is freely filtered by the glomerulus, enters the tubule epithelial cell through endocytosis, and is metabolized. It appears in the urine only when the renal threshold of 0.5 to 1.5 mg of myoglobin per deciliter is exceeded and is grossly visible as reddish-brown ("tea-colored") urine when serum myoglobin levels reach 100 mg per deciliter[15]; therefore, not all cases of rhabdomyolysis are associated with myoglobinuria.

Although the exact mechanisms by which rhabdomyolysis impairs the glomerular filtration rate are unclear, experimental evidence suggests that intrarenal vasoconstriction, direct and ischemic tubule injury, and tubular obstruction all play a role (Fig. 2).[16] Myoglobin becomes concentrated along the renal tubules, a process that is enhanced by volume depletion and renal vasoconstriction, and it precipitates when it interacts with the Tamm–Horsfall protein, a process favored by acidic urine.[17] Tubule obstruction occurs principally at the level of the distal tubules, and direct tubule cytotoxicity occurs mainly in the proximal tubules.

Myoglobin seems to have no marked nephrotoxic effect in the tubules unless the urine is acidic. Myoglobin is a heme protein; it contains iron, as ferrous oxide (Fe^{2+}), which is necessary for the binding of molecular oxygen. However, molecular oxygen can promote the oxidation of Fe^{2+} to ferric oxide (Fe^{3+}), thus generating a hydroxyl radical. This oxidative potential is counter-

acted by effective intracellular antioxidant molecules. However, cellular release of myoglobin leads to uncontrolled leakage of reactive oxygen species, and free radicals cause cellular injury. It has been suggested that heme and free iron–driven hydroxyl radicals are critical mediators of tubule damage owing to the protective effects of deferoxamine (an iron chelator) and glutathione.[18] More recently, it has been shown that myoglobin itself can exhibit peroxidase-like enzyme activity that leads to uncontrolled oxidation of biomolecules, lipid peroxidation, and the generation of isoprostanes.[19]

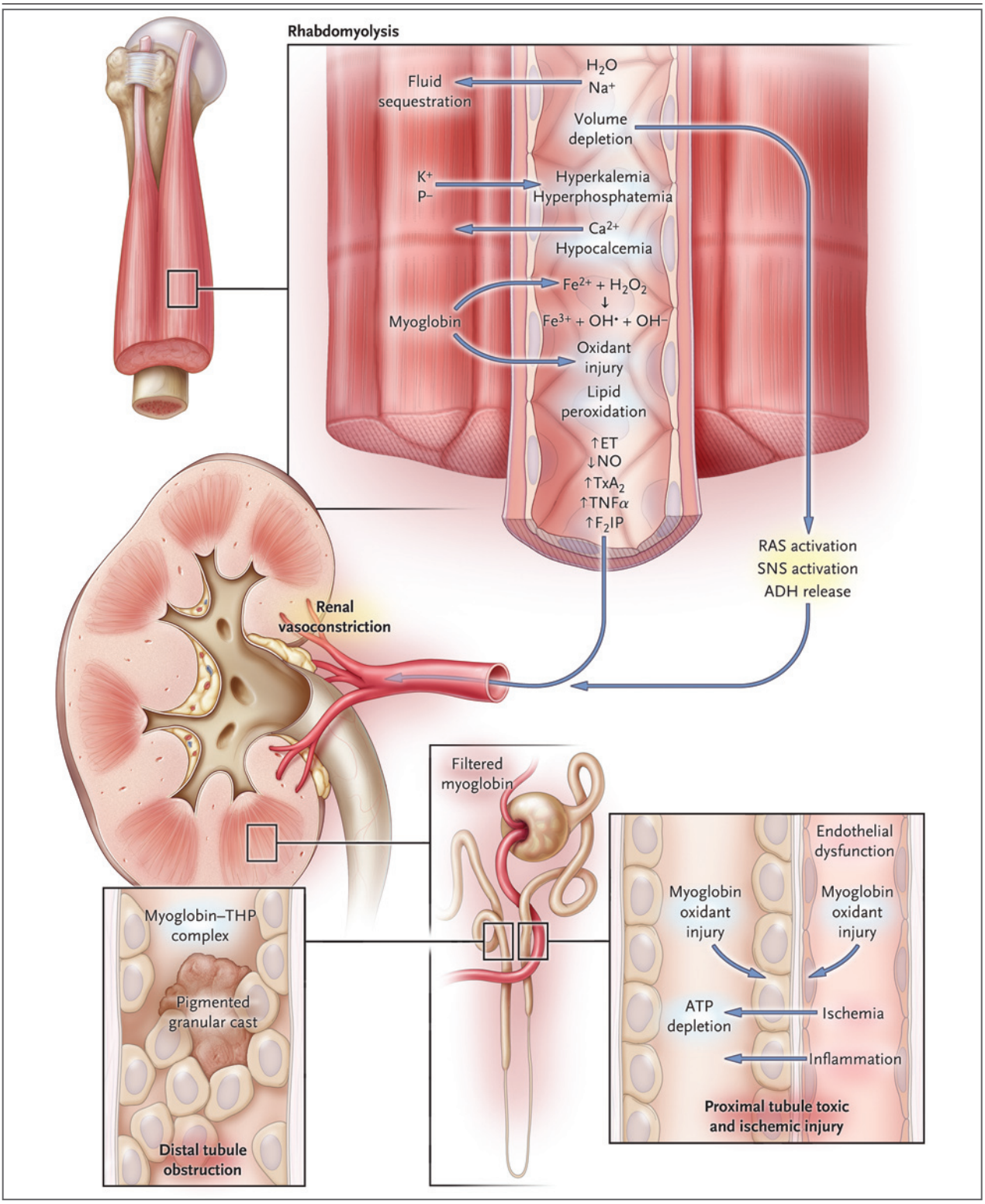
Renal vasoconstriction is a characteristic feature of rhabdomyolysis-induced acute kidney injury and is the result of various combinations of several mechanisms. First, intravascular volume depletion due to fluid sequestration within damaged muscle promotes homeostatic activation of the renin–angiotensin system, vasopressin, and the sympathetic nervous system. Second, experimental studies have shown that there are additional vascular mediators in the reduction of renal blood flow, including endothelin-1, thromboxane A_2, tumor necrosis factor α; and F_2-isoprostanes[9,20]; a deficit in the vasodilator nitric oxide, which can be attributed to the scavenging effect of myoglobin in the renal microcirculation, has also been shown to be a mediator in the reduction in renal blood flow.[16] Collectively, these vascular mediators appear to be locally stimulated by oxidant injury and leukocyte-mediated inflammation as a result of the endothelial dysfunction that is common to other forms of acute kidney injury.[21]

RENAL MANIFESTATIONS OF RHABDOMYOLYSIS

Patients with acute rhabdomyolysis usually present with pigmented granular casts, reddish-brown urine supernatant, and markedly raised serum creatine kinase. There is no defined threshold value of serum creatine kinase above which the risk of acute kidney injury is markedly increased. A very weak correlation between the peak creatine kinase value and the incidence of acute kidney injury or peak serum creatinine has been reported.[10,11,22] The risk of acute kidney injury in rhabdomyolysis is usually low when creatine kinase levels at admission are less than 15,000 to 20,000 U per liter.[12,13,23] Although acute kidney injury may be associated with creatine kinase values as low as 5000 U per liter, this usually occurs when coexisting conditions such as sepsis, dehydration, and acidosis are present.[11] For example, in patients with chronic myopathies such as muscular dystrophies and inflammatory myopathies, acute kidney injury seldom develops unless a superimposed event is present. Patients with these chronic myopathies, on the other hand, may have moderately raised concentrations of plasma myoglobin but not overt myoglobinuria.[24] Myoglobinuria can be inferred if urinary dipstick testing shows a positive result for blood when there are no red cells in the sediment. This false positive result for blood occurs because the dipstick test is unable to distinguish between myoglobin and hemoglobin. The test has a sensitivity of 80% for the detection of rhabdomyolysis.[10] Other causes of pigmented urine should be taken into consideration (Table 2).[25] Myoglobin is the true pathogenic factor in rhabdomyolysis-induced acute kidney injury but is seldom measured directly in urine or plasma. Serum myoglobin levels peak well before serum creatine kinase levels, and serum myoglobin has a rapid and unpredictable metabolism, which functions partly through the kidney but mainly outside the kidney (probably through the liver or spleen).[26] Therefore, measurement of serum myoglobin has a low sensitivity for the diagnosis of rhabdomyolysis.[27]

Acute kidney injury associated with rhabdomyolysis often leads to a more rapid increase in plasma creatinine than do other forms of acute kidney injury. However, this finding may reflect the overrepresentation of young, muscular men among patients with rhabdomyolysis rather than increased creatinine or creatine release from injured muscle.[14,28,29] Similarly, a low ratio of blood urea nitrogen to creatinine is often seen in patients with rhabdomyolysis. Rhabdomyolysis-induced acute kidney injury frequently causes oliguria and occasionally causes anuria.

Another characteristic feature of rhabdomyolysis-induced acute kidney injury that is different from the manifestation of other forms of acute tubular necrosis is the frequent, but not universal, presence of a low fractional excretion of sodium (<1%), perhaps reflecting the primacy of preglomerular vasoconstriction and tubular occlusion rather than tubular necrosis.[30] The fractional excretion of sodium is a measurement of the percentage of filtered sodium that is excreted in the urine, and low levels in patients with acute kidney injury are an indication of the relative



integrity of tubular functions. However, when ischemic or toxic acute tubular necrosis is established, both urinary sodium and the fractional excretion of sodium are raised.

Electrolyte abnormalities that occur as a result of the release of cellular components often accompany and determine the severity of rhabdomyolysis-induced acute kidney injury. Because

Table 2. Causes and Microscopic Features of Red and Brown Urine.

Cause	Results of Test for Blood in Fresh Urine*	Sediment†‡	Supernatant‡
Hematuria	+ to ++++	Red	Yellow
Myoglobinuria	+ to ++++	Normal	Red to brown
Hemoglobinuria	+ to ++++	Normal	Red to brown
Porphyria	Negative	Normal	Red
Bile pigments	Negative	Normal	Brown
Food and drugs§	Negative	Normal	Red to brown

* Urine was tested with the use of a dipstick test. This is a semiquantitative test of the number of erythrocytes per microliter. Results range from + (5 to 10 erythrocytes per microliter) to ++++ (approximately 250 erythrocytes per microliter).
† Normal refers to white or yellow in color, unremarkable in the absence of cells, crystals, or cylinders.
‡ The sediment and supernatant were examined after centrifugation of 10 to 15 ml of urine at 1500 to 3000 rpm for 5 minutes.
§ Food and drugs that can cause red urine include beets, blackberries, rhubarb, food coloring, fava beans, phenolphthalein, rifampin, doxorubicin, deferoxamine, chloroquine, ibuprofen, and methyldopa. Those that can cause brown urine include levodopa, metronidazole, nitrofurantoin, iron sorbitol, chloroquine, and methyldopa.

they may precede the acute kidney injury, electrolyte levels should be measured as soon as rhabdomyolysis is diagnosed. The electrolyte abnormalities that can occur with rhabdomyolysis include hyperkalemia (which can be rapidly increasing), hyperphosphatemia, hyperuricemia, high anion-gap metabolic acidosis, and hypermagnesemia mainly when renal failure is present.[4,15,22,31] High levels of phosphate can bind to calcium, and deposition of calcium–phosphate complexes in soft tissues can occur. In addition, hyperphosphatemia inhibits 1α-hydroxylase, thus limiting the formation of calcitriol (1,25-dihydroxyvitamin D_3), the active form of vitamin D. Hyperkalemia is an early manifestation of rhabdomyolysis, and serum potassium can occasionally reach life-threatening levels both in patients with severe traumatic rhabdomyolysis and in those with nontraumatic rhabdomyolysis.[15,31] Hyperuricemia is also usually present owing to the liberation of nucleosides from injured muscle and can contribute to renal tubule obstruction since uric acid is insoluble and may precipitate in acidic urine.

Hypocalcemia is a common complication of rhabdomyolysis and usually results from calcium entering the ischemic and damaged muscle cells and from the precipitation of calcium phosphate with calcification in necrotic muscle. Hypercalcemia associated with recovery of renal function is unique to rhabdomyolysis-induced acute kidney injury and results from the mobilization of calcium that was previously deposited in muscle, the normalization of hyperphosphatemia, and an increase in calcitriol.[32]

Figure 2 (facing page). Pathophysiological Mechanisms in Rhabdomyolysis-Induced Acute Kidney Injury.

Fluid sequestration in injured muscle induces volume depletion and consequent activation of the sympathetic nervous system (SNS), antidiuretic hormone (ADH), and the renin–angiotensin system (RAS), all of which favor vasoconstriction and renal salt and water conservation. In addition, myoglobin-induced oxidative injury increases vasoconstrictors and decreases vasodilators. Kidney injury results from a combination of ischemia due to renal vasoconstriction, direct tubular toxicity mediated by myoglobin-associated oxidative injury (inset, lower right), tubular damage due to ischemia, and distal tubule obstruction due to precipitation of the Tamm–Horsfall protein–myoglobin complex (inset, lower left) in addition to sloughed tubular cells forming cellular cast. As in acute kidney injury due to other causes, endothelial dysfunction and local inflammation contribute to tissue damage and organ dysfunction. ET denotes endothelin, F_2 IP F_2 isoprostanes, NO nitric oxide, THP Tamm–Horsfall protein, TNF-α tumor necrosis factor α, TxA_2 thromboxane A_2, and VC vasoconstriction.

TREATMENT AND PREVENTION

Patients with rhabdomyolysis that is associated with acute kidney injury usually present with a clinical picture of volume depletion that is due to the sequestration of water in injured muscles. Therefore, the main step in managing the condition (Table 3) remains the early, aggressive repletion of fluids; patients often require about 10 liters of fluid per day,[31] with the amount administered depending on the severity of the rhabdomyolysis.[33] There are no randomized trials that have evaluated fluid repletion in patients with the crush syndrome resulting from injuries sus-

Table 3. Steps in the Prevention and Treatment of Rhabdomyolysis-Induced Acute Kidney Injury.

Check for extracellular volume status, central venous pressure, and urine output.*
Measure serum creatine kinase levels. Measurement of other muscle enzymes (myoglobin, aldolase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) adds little information relevant to the diagnosis or management.
Measure levels of plasma and urine creatinine, potassium and sodium, blood urea nitrogen, total and ionized calcium, magnesium, phosphorus, and uric acid and albumin; evaluate acid–base status, blood-cell count, and coagulation.
Perform a urine dipstick test and examine the urine sediment.
Initiate volume repletion with normal saline promptly at a rate of approximately 400 ml per hour (200 to 1000 ml per hour depending on the setting and severity), with monitoring of the clinical course or of central venous pressure.
Target urine output of approximately 3 ml per kilogram of body weight per hour (200 ml per hour).
Check serum potassium level frequently.
Correct hypocalcemia only if symptomatic (e.g., tetany or seizures) or if severe hyperkalemia occurs.
Investigate the cause of rhabdomyolysis.
Check urine pH. If it is less than 6.5, alternate each liter of normal saline with 1 liter of 5% dextrose or 0.45% saline plus 100 mmol of bicarbonate. Avoid potassium and lactate-containing solutions.
Consider treatment with mannitol (up to 200 g per day and cumulative dose up to 800 g). Check for plasma osmolality and plasma osmolal gap. Discontinue if diuresis (>20 ml per hour) is not established.
Maintain volume repletion until myoglobinuria is cleared (as evidenced by clear urine or a urine dipstick testing result that is negative for blood).
Consider renal-replacement therapy if there is resistant hyperkalemia of more than 6.5 mmol per liter that is symptomatic (as assessed by electrocardiography), rapidly rising serum potassium, oliguria (<0.5 ml of urine per kilogram per hour for 12 hours), anuria, volume overload, or resistant metabolic acidosis (pH <7.1).

* In the case of the crush syndrome (e.g., earthquake, building collapse), institute aggressive volume repletion promptly before evacuating the patient.

tained in a disaster such as an earthquake. However, most, if not all, reports show that patients in whom acute kidney injury developed had a longer delay in receiving supportive therapy than did patients in whom acute kidney injury did not develop (Table 4).[8,23,31,33,39] Therefore, early, aggressive volume repletion is crucial in patients with the crush syndrome.[34,35]

Although the need for volume repletion is established, the composition of the fluid used for repletion remains controversial. Some investigators recommend administering sodium bicarbonate, which results in an alkaline urine, as first proposed by Bywaters and Beall,[8,39,40] whereas others argue against this approach and favor normal or 0.45% saline solution.[15] The three empirical advantages of alkalinization that have been noted are based on studies in animal models of rhabdomyolysis. First, it is known that precipitation of the Tamm–Horsfall protein–myoglobin complex is increased in acidic urine.[17] Second, alkalinization inhibits reduction–oxidation (redox) cycling of myoglobin and lipid peroxidation in rhabdomyolysis, thus ameliorating tubule injury.[41] Third, it has been shown that metmyoglobin induces vasoconstriction only in an acidic medium in the isolated perfused kidney.[42] The principal, and probably the only, disadvantage of alkalinization is the reduction in ionized calcium, which can exacerbate the symptoms of the initial hypocalcemic phase of rhabdomyolysis.

The clinical benefits of alkalinization as compared with simple volume repletion are not firmly established. Comparative studies usually have small sample sizes and show a combination of measures (e.g., alkalinization plus mannitol) that preclude an analysis of the effectiveness of the particular single measure[34-38] (Table 4). In one study, renal outcomes did not differ significantly between patients treated with bicarbonate plus mannitol and those treated with saline alone, although peak serum creatine kinase values were below 5000 U per liter, a finding indicating that the degree of injury was mild, making treatment effect difficult to appreciate.[36] In the largest study of patients who had undergone trauma (2083 patients), rhabdomyolysis developed in 85% of the patients, and administration of bicarbonate plus mannitol did not prevent renal failure, the need for dialysis, or death in the sample as a whole, although the results suggested that it might be beneficial in patients with peak creatine kinase

Table 4. Comparative Studies on Preventive and Therapeutic Regimens in Rhabdomyolysis.

Study	Study Design	Patient Group	No. in Sample	Therapeutic Strategy	Outcome in Patients with Acute Kidney Injury
Shimazu et al.[34]	Retrospective	Patients with the crush syndrome	14	Late vs. early initiation of therapy; high (>10 liters for 48 hours) vs. low volume of hydration	Better if therapy initiated early; high volume of hydration better
Gunal et al.[35]	Retrospective	Patients with the crush syndrome	16	Early vs. late treatment with normal saline followed immediately by bicarbonate	Better if treatment initiated early
Homsi et al.[36]	Retrospective	Patients in the intensive care unit	24	Normal saline vs. normal saline plus bicarbonate and mannitol	No difference
Brown et al.[37]	Retrospective	Patients with trauma	2083	Normal saline vs. bicarbonate plus mannitol	No difference
Cho et al.[38]	Prospective, randomized	Patients with intoxication from doxylamine	28	Ringer's lactate vs. normal saline; bicarbonate if urine pH is <6.5	No effect on peak creatine kinase level or recovery with Ringer's lactate as compared with normal saline; more bicarbonate needed with normal saline than with Ringer's lactate

values of more than 30,000 U per liter.[37] In a randomized, prospective trial of fluid repletion with Ringer's lactate as compared with normal saline in patients with rhabdomyolysis attributed to doxylamine intoxication, 28 patients were randomly assigned to receive one of the solutions.[38] Sodium bicarbonate was added in both groups if the urine pH was less than 6.5 after 12 hours of aggressive volume repletion. Peak creatine kinase levels were less than 10,000 U per liter, and it appears that acute kidney injury did not develop in any of the patients, although these data were not reported. Whatever the real, consistent benefits of urine alkalinization in patients with rhabdomyolysis, there is evidence that massive infusion of normal saline alone can contribute to metabolic acidosis, mainly owing to the dilution of serum bicarbonate with a solution relatively high in chloride ions, generating hyperchloremic metabolic acidosis with observed reductions in serum pH of as much as 0.30 units.[43] Therefore, administration of both normal saline and sodium bicarbonate seems to be a reasonable approach when fluid is being replenished in patients with rhabdomyolysis, especially patients with metabolic acidosis (Table 3). If sodium bicarbonate is used, urine pH and serum bicarbonate, calcium, and potassium levels should be monitored, and if the urine pH does not rise after 4 to 6 hours of treatment or if symptomatic hypocalcemia develops, alkalinization should be discontinued and hydration continued with normal saline.

The use of diuretics remains controversial, but it is clear that it should be restricted to patients in whom the fluid repletion has been achieved. Mannitol may have several benefits: as an osmotic diuretic, it increases urinary flow and the flushing of nephrotoxic agents through the renal tubules; as an osmotic agent, it creates a gradient that extracts fluid that has accumulated in injured muscles and thus improves hypovolemia; finally, it is a free-radical scavenger.[4,8,20] Most data on the action of mannitol come from studies in animals, which collectively show that the protective effect of mannitol may be attributable to its osmotic diuretic action rather than to the other mechanisms.[44] No randomized, controlled trial has supported the evidence-based use of mannitol, and some clinical studies suggest no beneficial effects.[36,37] In addition, high accumulated doses of mannitol (>200 g per day or accumulated doses of >800 g) have been associated with acute kidney injury due to renal vasoconstriction and tubular toxicity, a condition known as osmotic nephrosis.[45,46] However, many experts continue to suggest that mannitol should be used to prevent and treat rhabdomyolysis-induced acute kidney injury and relieve compartmental pressure.[20,45-47] During the time mannitol is being administered, plasma osmolality and the osmolal gap (i.e., the difference between the measured and calculated serum osmolality) should be monitored frequently and therapy discontinued if adequate diuresis is not achieved or if the osmolal gap rises above 55 mOsm per kilogram.[46] Loop

Table 5. Approach to the Management of Hyperkalemia (Serum Potassium ≥5.5 mmol per Liter) in Rhabdomyolysis.

Check for potassium levels every 4 hours in cases of severe rhabdomyolysis (creatine kinase level >60,000 to 80,000 U per liter) or suspected systemic toxin. Treat rapidly rising potassium levels aggressively.
Obtain an electrocardiogram and check for severe manifestations (QRS interval widening, small P waves, severe arrhythmias thought to be caused by high levels of potassium). Consider cardiac monitoring and admission to an intensive care unit if the potassium level is higher than 6 mmol per liter, if there are abnormalities on the electrocardiogram, or if rhabdomyolysis is severe, with rapidly rising potassium.
Check for plasma calcium levels. Hypocalcemia seriously aggravates the adverse electrical effects of hyperkalemia.
If the electrocardiogram shows severe irregularities, administer calcium chloride or calcium gluconate by intravenous infusion. Consider slow continuous infusion if hypocalcemia is present. Anticipate possible hypercalcemia in late rhabdomyolysis. Do not mix with bicarbonate solutions.
If potassium level is higher than 6 mmol per liter, shift potassium into cells. Serum potassium will be lowered approximately 10 to 30 minutes after the following measures are performed, and the effect will last for 2 to 6 hours.
Administer insulin and glucose by means of a slow intravenous push; monitor glucose with the use of fingerstick testing.
Administer a β_2-adrenergic agonist such as albuterol, 10 to 20 mg in 4 ml of normal saline by inhalation of aerosol over 10 minutes. Do not use as a single measure; combine with glucose and insulin for additive effect.
Administer sodium bicarbonate if the patient has acidemia. This treatment may worsen the manifestations of hypocalcemia, and the efficacy is not as consistent as that with insulin and glucose or albuterol. Do not use as a single measure.
Remove potassium from the body with the use of either resins or dialysis as indicated; the use of diuretics is optional.
Administer cation-exchange resin (sodium polystyrene sulfonate) orally or as a retention enema (avoid sorbitol in such cases and avoid after surgery).
Perform hemodialysis if the above measures fail or if severe renal failure or severe hyperkalemia develops. Consider hemodialysis when rhabdomyolysis is associated with marked tissue breakdown and rapidly rising serum potassium levels. Check serum potassium levels 4 hours after hemodialysis, since a rebound increase can occur. Previous measures of potassium shift into cells may decrease the efficiency of hemodialysis with respect to removal of potassium.
Administer loop diuretics such as furosemide, but only after the patient's fluid level has been expanded.

diuretics also increase urinary flow and may decrease the risk of myoglobin precipitation, but no study has shown a clear benefit in patients with rhabdomyolysis. Therefore, loop diuretics in rhabdomyolysis-induced acute kidney injury should be used in the same manner as that recommended in acute kidney injury that is due to other causes.[47,48]

The electrolyte abnormalities associated with rhabdomyolysis-induced acute kidney injury must be treated promptly; the correction of hyperkalemia, which occurs very early in the course of the disease, is especially important (Table 5).[49] Agents that cause a shift of potassium from the extracellular to the intracellular space (e.g., hypertonic glucose and bicarbonate) are effective only temporarily, and the only means of removing potassium from the body is diuresis (effective kaliuresis), the use of intestinal potassium binders, or dialysis.[4,8,9,15] In contrast, early hypocalcemia should not be treated unless it is symptomatic or unless severe hyperkalemia is present. Calcium-containing chelators should be used with caution to treat hyperphosphatemia, since the calcium load could increase the precipitation of calcium phosphate in injured muscle.[4,8,9,15]

When acute kidney injury is severe enough to produce refractory hyperkalemia, acidosis, or volume overload, renal-replacement therapy is indicated, principally with intermittent hemodialysis, which can correct electrolyte abnormalities rapidly and efficiently.[8,9,47] Conventional hemodialysis does not remove myoglobin effectively owing to the size of the protein and is therefore usually mandated by renal indications. However, owing to the pathogenic role of myoglobin in rhabdomyolysis-induced acute kidney injury, preventive extracorporeal elimination has been studied. Although plasmapheresis has been shown to have no effect on outcomes or on the myoglobin burden of the kidneys,[50] continuous venovenous hemofiltration or hemodiafiltration has shown some efficacy in removing myoglobin, principally with the use of super high-flux filters and high volumes of ultrafiltration (convection).[51] However, the evidence is mainly from isolated case reports, and the effect on outcomes is unknown. In addition, some studies have shown that the half-life of serum myoglobin does not differ significantly between patients who are treated conservatively and those who receive continuous venovenous hemodiafiltration.[27] Until randomized studies are performed, preventive hemofiltration cannot be recommended.

The use of antioxidants and free-radical scav-

engers (e.g., pentoxifylline, vitamin E, and vitamin C) may be justified in the treatment or prevention of myoglobinuric acute kidney injury,[8,52] as suggested by small case series, case reports, and various experimental studies of myoglobinuria, but controlled studies evaluating their efficacy are lacking.

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