# Rhabdomyolysis
## Evaluation and Emergent Management

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**Timely diagnosis and treatment of rhabdomyolysis can save lives and limbs, as well as preserve renal function. This article delineates causes and features of the syndrome and summarizes evaluation and management considerations.**

Rhabdomyolysis is a clinical syndrome caused by insults to myocytes and muscle membranes that lead to the destruction of skeletal muscle and release of muscle fiber contents into the bloodstream.[1,2] The insults that may lead to rhabdomyolysis range from direct muscle trauma—which is the most common cause—to genetic causes (enzyme deficiencies), toxins (including illicit drugs), infections, and endocrinologic etiologies (eg, diabetic ketoacidosis, hyperosmolar nonketotic states, and hypothyroidism).[3] The most sensitive indicator of rhabdomyolysis is an elevated serum creatine kinase (CK) level. In the absence of brain or cardiac issues, a CK concentration of 5,000 U/L or greater (with 50 to 250 U/L considered the normal range) is indicative of significant muscle injury.[4]

The clinical spectrum of rhabdomyolysis ranges from mild illness with minimal elevation of serum CK measurements to substantially elevated levels of muscle breakdown products with electrolyte imbalances, subsequent renal failure secondary to myoglobinuria, and the potential for disseminated intravascular coagulation (DIC). Approximately 10% to 50% of patients with rhabdomyolysis develop acute renal failure,[5] and some reports indicate that rhabdomyolysis causes 5% to 25% of cases of acute renal failure.[5-7] There is a high prevalence of rhabdomyolysis in patients with acute traumatic injuries, and mortality in those patients with severe injury who develop renal failure is around 20%.[8]

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### ETIOLOGY AND PATHOPHYSIOLOGY

Rhabdomyolysis has many etiologies, which can be loosely separated into physical and nonphysical causes. Physical causes are acquired, while nonphysical causes are typically inherited; however, nonphysical causes also include toxins, drugs, infections, and electrolyte imbalances.[4] Some physical etiologies of rhabdomyolysis that are seen in the emergency department include exercise, prolonged immobilization, and trauma and compression. Use of recreational drugs (eg, cocaine, amphetamines, opiates, and other stimulants) is a notable nonphysical cause.[9] Lipid-lowering agents, espe-

cially statins, also can induce rhabdomyolysis.[10]

Cocaine use and abuse deserves special mention because it is both a physical and nonphysical cause of rhabdomyolysis. Acute rhabdomyolysis is seen in almost one-fourth of patients presenting to the emergency department with cocaine-associated disorders.[4,11] A mechanism by which cocaine is thought to produce the syndrome is muscle ischemia resulting from its prolonged vasoconstrictive effect. Cocaine is also thought to have a direct toxic effect on myofibrils. The physical effects of cocaine can be caused by generalized tonic-clonic seizures and compression of muscle tissue subsequent to a seizure.[12]

There are several purported mechanisms of renal failure in rhabdomyolysis. In addition to the direct toxic effects of myoglobin on the renal tubules, vasoconstriction due to a low-flow state caused by volume depletion produces tubular obstruction and further damage. Volume depletion may be due to a myriad of factors, depending upon the clinical scenario. A cascade of events ensues, including the production of renal vasoconstrictors. This, along with a relative reduction of the renal vasodilator nitric oxide (due to volume depletion), ultimately leads to renal ischemia, and kidney damage is further compounded.[5,13]

**FAST TRACK**

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## Physical Causes

*Hyperthermic Syndromes*—The hyperthermic syndromes include exertional heat stroke, malignant hyperthermia, neuroleptic malignant syndrome (NMS), and serotonin syndrome. (See "Case Studies in Toxicology: Toxicologic Hyperthermia" in the November 2011 issue of *Emergency Medicine* [pp 13-16].) Exertional heat stroke presents with muscle weakness, fever, delirium, seizures, and coma. Sweating may or may not occur. This syndrome is caused by activities that increase heat production. The late sequelae of heat stroke include hypotension, hypoglycemia, lactic acidosis, and DIC, which may ultimately be followed by multiorgan failure.[14] Management of heat stroke entails removal of specific inciting events to initiate cooling and reverse the process, along with supportive care, which at times may be intensive. Hypokalemia worsens rhabdomyolysis and increases the risk of developing heat stroke.[14] Malignant hyperthermia occurs most often in the setting of general anesthesia but can be seen with exposure to other nonanesthetic agents, including gasoline vapors and certain decongestants.[15-18] This syndrome consists of skeletal muscle rigidity, fever, hemodynamic collapse, hyperventilation, tachycardia, and cyanosis, with rising end-expiratory carbon dioxide concentration and lactic acidosis.[15,19] Rhabdomyolysis secondary to NMS is caused by the production of heat from muscle rigidity and tremor, both of which occur due to central dopaminergic blockade.[20] A mimic of NMS is the serotonin syndrome. This syndrome features an altered mental status and neuromuscular irritability with autonomic instability,[21] and it can be associated with myoglobinuric renal failure.[22] These syndromes can be differentiated based on the history and the context in which the syndrome has occurred, along with the absence of muscular rigidity in exertional heat stroke.[23]

*Exercise*—It has long been known that elevations of CK can result from moderate exercise, with associated myoglobinemia and myoglobinuria.[24] In extreme circumstances, as in the case of tremendous physical exertion, muscle necrosis can occur, resulting in severe rhabdomyolysis. This effect may be potentiated by high ambient temperatures.[25] The purported mechanism is a combination of direct muscle injury and thermal damage. Medical conditions that can cause muscle damage by this mechanism include status epilepticus and myoclonus.[26]

*Lightning and Electrical Injury*—Rhabdomyolysis following lightning strikes and electrical injuries is seen in approximately 10% of patients that survive the initial injury.[27] In this context, rhabdomyolysis presents with a natural history similar to that associated with

untreated crush injuries (ie, hypotension and circulatory shock, muscle swelling, and acute myoglobinuric renal failure[28]), and its extent is not associated with the size of the wounds or the site of entry.[29,30]

## Nonphysical Causes

*Electrolyte Abnormalities*—Electrolyte abnormalities are also associated with rhabdomyolysis. Hypokalemia, hyponatremia, and hypophosphatemia are well-known examples.[6] Rhabdomyolysis can result from excessive use of diuretics or cathartic drugs, as well as from any malady that produces significant electrolyte losses (eg, persistent vomiting, as in hyperemesis gravidarum) leading to depletion of total body potassium.[31,32]

*Infectious*—Infectious etiologies, such as influenza A and B, *Legionella*, *Streptococcus*, and *Salmonella*, have been noted as a potential cause of rhabdomyolysis. The exact mechanism is unknown, but putative mechanisms include damage caused by fever, invasion of muscle by the organism,[33] and toxin generation,[33] as well as the effects of the treatment given for the infection. Affected patients can present with local signs of infection with muscle tenderness, erythema, and edema.[34]

**FAST TRACK**

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*Genetic*—Inherited defects of muscle metabolism can cause recurrent episodes of myoglobinuria, and these episodes can be precipitated by exercise, infection, or malnutrition. Combined defects have also been described. These syndromes include mitochondrial cytopathies, fatty acid oxidation disorders, and idiopathic recurrent myoglobinuria.[35-37]

*Alcoholism*—Alcohol is a direct membrane toxin that increases permeability into and out of the cell. Muscle biopsy findings in patients with chronic alcoholism demonstrate elevations of sodium, calcium, chloride, and water content, along with concomitant decreases in potassium, magnesium, and phosphorus

levels.[38] Rhabdomyolysis can occur after an alcohol binge or other such prolonged periods of alcohol intake.

## CLINICAL FEATURES

The clinical syndrome of rhabdomyolysis classically presents with a triad of features: muscle aches and pains, weakness, and tea-colored urine.[39] The finding of reddish-brown urine typically associated with rhabdomyolysis does not occur until serum myoglobin levels reach 100 mg/dL.[40] In one pediatric study, dark (ie, tea-colored) urine was reported in less than 4% of cases of documented rhabdomyolysis.[41] The muscle symptoms may be generalized or localized to specific muscle groups. The most commonly affected groups are those in the calves and the lower back.[42] In fact, due to the localizing nature of rhabdomyolysis, clinicians may mistakenly begin investigations into other etiologies of calf and back pain, such as deep venous thrombosis, pyelonephritis, and renal colic, respectively. Furthermore, about half of patients do not report any muscle pain or weakness.[43] In addition to muscle swelling and tenderness, there may be physical changes seen in the skin (ie, pressure necrosis). The classic triad should not be relied upon to diagnose rhabdomyolysis, as these features are seen in only 10% of patients presenting with the condition.[39,44] Systemic symptoms and signs of rhabdomyolysis include fever, malaise, nausea, and vomiting. Patients may have clinical signs of dehydration and may be tachycardic.

**FAST TRACK**

*Grossly visible myoglobinuria does not manifest until at least 100 g of muscle is destroyed; thus, early measurement of serum and urine myoglobin is essential.*

## LABORATORY EVALUATION

Laboratory investigation is important in the diagnosis of rhabdomyolysis. Leukocytosis and myoglobinuria may be seen in affected patients. Destruction of myocytes leads to leakage of intracellular contents, including CK and potassium, into the circulatory system. The most sensitive marker for significant muscle injury is a CK level five times above normal in the absence of cardiac or brain injury.[45] However, the rise in serum myoglobin precedes the rise in CK. Grossly visible myoglobinuria does not manifest until approximately 100 g or more of muscle is destroyed[46]; therefore, measurement of serum and urine myoglobin is essential for the early diagnosis of rhabdomyolysis. Urinalysis results will be positive for hemoglobin, and yet no red blood cells will be found on microscopic examination. Additional laboratory findings in rhabdomyolysis include elevated serum potassium concentrations (potassium levels may rise with progression of the process), either hypocalcemia or hypercalcemia, hyperphosphatemia, and elevated liver enzyme levels (which occur in 25% of patients with rhabdomyolysis).[40] Typically, through the course of the process, serum potassium and phosphate levels increase as myocytes are destroyed, and later decrease due to excretion by the kidneys. The mechanism of severe hyperkalemia is twofold. Hyperkalemia may be caused by leakage from damaged myocytes as well as the reduction in glomerular filtration rate secondary to acute renal failure. The acute rise in serum potassium may potentiate cardiac arrhythmias and subsequent cardiac arrest.[39] Calcium levels may initially decrease due to cell membrane destruction and calcium intrusion into cells, and then gradually increase due to reequilibration.[47] Later findings (occurring 12 to 72 hours after the initial process) may include thrombocytopenia, elevated creatinine concentrations, and evidence of DIC.[1]

## MANAGEMENT

Foremost in the treatment of this condition is resuscitation of the patient. Airway, breathing, and circulation must be promptly evaluated and the patient stabilized. In addition, consideration must be given to the preservation of renal function.[48] Aggressive fluid replacement is key in preserving renal function, and the greater the delay in rehydration, the greater the possibility of renal failure.[4,49] There are no specific data on how much fluid should be used in volume loading, but an initial 10- to 20-mL/kg IV bolus should be considered. This should be repeated as needed. In all patients, the initial bolus

should be followed by maintenance fluids to maintain a urine output of 1 to 2 mL/kg/h. Forced diuresis initiated within 6 hours of admission may reduce the risk of acute renal failure.[4,13]

Mannitol has also been used to prevent renal damage. However, there is minimal evidence of the superiority of this agent over aggressive fluid resuscitation. Some studies have indicated that saline alone prevents progression to renal failure, with no benefit at all from mannitol and sodium bicarbonate.[4,50-52] Furthermore, mannitol infusion has been associated with complications due to hypernatremia, hyperosmolarity, and extracelluar fluid shifts, especially in the brain.[53] At large doses (especially in patients who have not had adequate fluid replacement), mannitol may actually worsen renal failure.[39]

Urinary alkalinization (achieving a urinary pH >6.5 by the infusion of sodium bicarbonate alone or with saline) theoretically reduces urinary cast formation in animal models and prevents oxidative injury to the kidneys.[4,54] Unfortunately, many of the same studies refuting mannitol as a reasonable treatment option have also failed to demonstrate any benefit from urinary alkalinization in the prevention of acute renal failure.[51] However, alkalinizing the urine has not been shown to cause harm. Caution should be exercised if urinary pH is above 7.5 or the initial urinary sodium bicarbonate level is above 30 mEq/L. Furthermore, sodium bicarbonate should be administered only after the patient has undergone appropriate volume loading and demonstrated adequate urine output (1 to 2 mL/kg/h).

If renal failure has developed, especially with the onset of severe acidosis and hyperkalemia, hemodialysis may be required. Initially, daily hemodialysis or continuous hemofiltration[55] may be necessary to remove the byproducts of myocyte necrosis, allowing for correction of fluid overload and the removal of solutes. It is critical to normalize potassium levels due to the potential of early hyperkalemia to promote cardiac arrhythmias and possibly cardiac arrest.

Since hypercalcemia occurs during recovery in approximately 25% of patients with renal failure resulting from rhabdomyolysis, it is imperative to avoid the administration of calcium during the renal failure phase, except for symptomatic hypocalcemia or severe hyperkalemia.[4,56]

## CONCLUSION

Rhabdomyolysis can be a limb- and potentially life-threatening condition that must be evaluated in patients with a history of muscle injury. This muscle injury can arise from numerous causes. Common findings include muscle pain, tenderness, and weakness, along with a darkening of urine color. In addition, laboratory testing often reveals elevated serum CK levels, and urinalysis demonstrates hemoglobin without evidence of red blood cells. Aggressive fluid resuscitation is the standard of care, with initial boluses to maintain hemodynamic status and a urine output of 1 to 2 mL/kg/h. Sodium bicarbonate and mannitol, although used traditionally, have been shown to offer limited benefit. Hemodialysis is necessary if renal failure has occurred. **EM**

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