Series Editor: Mark A. Perazella, MD

Rhabdomyolysis

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A 32-year-old man with no significant past medical history presented to the emergency department with complaints of weakness, myalgias, and muscle stiffness. Physical examination was notable for a low-grade fever at 100.8°F, mild tachycardia at 110 bpm, and moderate tenderness on palpation of the muscle groups of the calves, thighs, biceps, triceps, and shoulder girdle. Cardiac auscultation revealed no murmurs, neurologic examination showed no focal deficits, and skin examination was normal. On further questioning, the patient admitted to using crack cocaine for 2 days. Notable laboratory values were as follows: a white blood cell count of 15,000 cells/μL (normal, 4500–11,000 cells/μL), creatine kinase level of 16,500 IU/L (normal, 40–150 IU/L), blood urea nitrogen level of 29 mg/dL (normal, 8–23 mg/dL), creatinine level of 1.1 mg/dL (normal, 0.6–1.2 mg/dL), and potassium level of 4.0 mEq/L (normal, 40–150 mEq/L). Urine myoglobin was not detected, urinalysis was normal, and urine toxicologic screen was positive for cocaine. Rapid influenza testing was negative. The patient was admitted to the medical floor with a diagnosis of cocaine-induced rhabdomyolysis.

Rhabdomyolysis is an uncommon disease process with profound sequelae if it is not identified and treated expediently. Approximately 26,000 cases of rhabdomyolysis are reported annually in the United States.[1] Rhabdomyolysis accounts for an estimated 8% to 15% of cases of acute renal failure and is associated with a mortality rate of 5%.[2,3] Morbidity and mortality are usually the result of hyperkalemia, metabolic acidosis, and acute renal failure. Clinical presentation varies, ranging from a nearly asymptomatic illness to a fulminant and life-threatening disease process with multiorgan system failure. This article reviews the pathophysiology, etiology, clinical features, and management of rhabdomyolysis.

PATHOPHYSIOLOGY

Rhabdomyolysis is a clinical syndrome caused by injury to striated muscle. Despite the numerous conditions that can cause rhabdomyolysis, there is a single common pathway involving injury to skeletal muscle, breakdown of the myocyte cell membrane, and release of intracellular contents into the extracellular fluid and circulation. The normal cellular function of the myocyte is maintained by ionic gradients generated by adenosine triphosphate (ATP)–dependent pumps embedded within the cell membrane. Sodium-potassium pumps maintain a low intracellular sodium level, which favors efflux of calcium in exchange for sodium by a separate ion exchange channel. Low intracellular calcium levels are also maintained by active sequestration into the sarcoplasmic reticulum and mitochondria.

Damage to the myocyte cell membrane may be caused directly through trauma (eg, crush injury) or indirectly through lack of adequate energy in the form of ATP (eg, vigorous sustained exercise). Regardless of the cause, damage to the sarcolemma leads to a loss of ionic gradients, thus increasing intracellular calcium.[4] This influx of calcium increases the activity of intracellular proteolytic enzymes that degrade the muscle cell. As the myocyte degenerates, intracellular compounds are extruded into the extracellular fluid and plasma. These compounds may include myoglobin, aldolase, potassium, uric acid, lactate dehydrogenase, aspartate transaminase, creatine kinase (CK), and phosphate.[5,6] In excess, these substances may have toxic effects on distant organ systems.

During myocyte destruction, the level of free myoglobin in the plasma increases, resulting in higher quantities of myoglobin that are filtered by the kidneys.[7] Myoglobinemia and myoglobinuria have long been associated with the development of acute kidney injury in rhabdomyolysis.[8] Myoglobin is directly toxic to renal tubular cells, a process that is likely mediated by

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TAKE HOME POINTS

- The single common pathophysiologic pathway in rhabdomyolysis involves damage to the myocyte cell membrane, extrusion of intracellular muscle contents into the circulation, and toxic effects on distant organ systems.
- The diagnosis of rhabdomyolysis is best achieved through careful clinical suspicion in combination with an elevated serum creatine kinase level.
- Renal injury may be averted through aggressive intravascular volume replacement, maintenance of high urinary flows, urinary alkalinization, and mannitol therapy.
- Indications for dialysis include refractory hyperkalemia, refractory acidosis, and volume overload.
- Early diagnosis, combined with aggressive treatment of complications, may decrease morbidity and mortality.

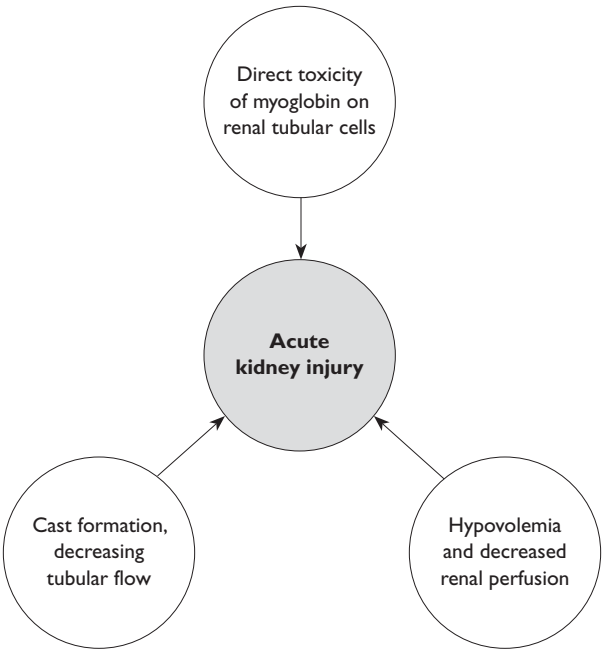

Figure. Etiology of acute kidney injury in patients with rhabdomyolysis.

free radicals.[9,10] In the presence of acidosis and hypovolemia, myoglobin reacts with Tamm-Horsfall protein and precipitates into casts, which may then obstruct tubular flow. Hypovolemia and overall decreased renal perfusion also can compound renal injury. The **Figure** depicts the multifactorial nature of acute kidney injury in rhabdomyolysis patients. Rhabdomyolysis-induced acute kidney injury is principally caused by damage to the renal parenchyma and is thus classified as acute intrinsic renal failure (AIRF). This syndrome is associated with a low specific gravity of urine, pigmented casts, and a high fractional excretion of sodium.

The release of intracellular electrolytes from dying myocytes may be life-threatening. Rapid release of intracellular potassium, especially in the setting of acute kidney injury and metabolic acidosis, may precipitate malignant cardiac dysrhythmias. Heart blocks, ventricular tachycardia, ventricular fibrillation, pulseless electrical activity, and asystole may occur with little warning. Intracellular phosphorus may rapidly precipitate in muscle tissues with calcium, which is reflected by the early development of hyperphosphatemia and hypocalcemia.

The hematologic system and clotting cascade also may be affected by rhabdomyolysis. Necrosis of muscle, in combination with release of tissue thromboplastin, may lead to disseminated intravascular coagulation (DIC) and hemorrhagic complications.[11] Aggressively monitoring for complications of rhabdomyolysis, such as DIC, is paramount to ensure their early detection (**Table 1**).

ETIOLOGY

In the United States, the most common causes of rhabdomyolysis are muscle overexertion, muscle compression, and the use of illicit drugs (eg, cocaine, amphetamines) or alcohol.[12] However, a myriad of etiologies has been reported as inciting factors. Traumatic causes of rhabdomyolysis include blunt trauma, crush injury, and strenuous exercise. Nontraumatic etiologies can be broadly divided into toxicologic, infectious, and metabolic causes. The classic case of crush injury leading to skeletal muscle destruction and rhabdomyolysis is a familiar textbook presentation. However, recognition of rhabdomyolysis caused by toxins, infections (eg, influenza, HIV), or hereditary metabolic myopathies requires a higher degree of clinical suspicion.

Toxins

As illustrated by the case presentation, cocaine is a common cause of rhabdomyolysis, particularly in urban patient populations. Cocaine-induced muscle injury may occur through multiple mechanisms: vasospasm with muscular ischemia, seizures, hyperpyrexia, coma with muscle compression, and direct myofibrillar damage.[13] In a series of patients with cocaine-induced rhabdomyolysis, 13 of 39 patients developed acute kidney

injury, the patients' mean CK level was 12,187 IU/L (range, 1756–85,000 IU/L), and 6 patients died.[14]

Numerous medications have been implicated in cases of rhabdomyolysis, including zidovudine, colchicine, isoniazid, opiates, benzodiazepines, corticosteroids, statins, and fibric acid derivatives. Statin drugs inhibit the 3-hydroxy-3-methylglutaryl coenzyme A reductase and are potent reducers of low-density lipoprotein cholesterol. As these drugs are commonly prescribed, they merit particular attention. In rare cases, statin drugs may cause myopathy and life-threatening rhabdomyolysis. The incidence of life-threatening rhabdomyolysis appears to be quite low with statin monotherapy (0.44 per 10,000 years of patient use), with the exception of cerivastatin, which was withdrawn from the market voluntarily by its manufacturer in 2001. Increased risk of developing rhabdomyolysis occurs in elderly persons, in diabetic patients, and when a statin is combined with a fibric acid derivative (5.98 per 10,000 years of patient use).[15] Statins block production of farnesyl pyrophosphate, an intermediate in the synthesis of coenzyme Q10 (Co Q10). Co Q10 is important in mitochondrial energy production. It has been hypothesized that statin-induced Co Q10 deficiency is involved in the pathogenesis of statin myopathy, and that supplemental Co Q10 may reduce risk in certain patient populations.[16]

Infections

The pathogenesis of rhabdomyolysis associated with infections (whether bacterial, viral, or fungal) is thought to be the result of direct cell invasion and cellular degeneration by the pathogen.[17] In adult patients, *Legionella* species are classically associated with rhabdomyolysis. Other bacteria linked to rhabdomyolysis include *Salmonella* species, group A β-hemolytic streptococci, *Francisella tularensis*, and *Escherichia coli*. Influenza A and B are the most common viruses associated with rhabdomyolysis, while HIV remains an important consideration. Studies estimate that up to 25% of AIDS patients suffer from a myopathic disease that may be complicated by rhabdomyolysis.[18]

Genetic Disorders

In cases where the etiology remains elusive, a genetic disorder should be considered. Genetic disorders should be suspected particularly in pediatric patients with recurrent rhabdomyolysis after minimal to moderate exertion or following a viral infection. Any genetic disorder associated with decreased energy production may cause rhabdomyolysis, which can include disorders of carbohydrate metabolism, fatty acid oxidation, nucleoside metabolism, myopathies, and mitochondrial defects.

Table 1. Complications Associated with Rhabdomyolysis

Acute renal failure
Disseminated intravascular coagulation
Electrolyte and metabolic derangements
Hypoalbuminemia
Hypocalcemia (early)
Hypercalcemia (late)
Hyperkalemia
Hypernatremia
Hyperphosphatemia
Hyperuricemia
Cardiac dysrhythmias
Compartment syndromes
Shock
Death

CLINICAL FEATURES

The clinical presentation of rhabdomyolysis is diverse. Some patients present with an acute medical or traumatic condition with rhabdomyolysis as a clear complication. In other patients, rhabdomyolysis may be found by laboratory testing alone, prompting a search for an inciting condition. Classically, patients with rhabdomyolysis report myalgias, muscle weakness and swelling, and dark-colored urine. Nonspecific systemic symptoms, such as malaise, fever, abdominal pain, and nausea and vomiting, may also be seen. Initial assessment of symptoms may prove difficult in patients with altered mental status, intoxication, electrolyte imbalance, or uremic encephalopathy.

Physical examination may show signs of dehydration, such as dry mucous membranes, decreased skin turgor, and delayed capillary refill. The overlying skin may be bruised or discolored if trauma has occurred. With the development of a compartment syndrome, the affected area may demonstrate pain on passive range of motion, sensory deficits, motor deficits, or signs of vascular insufficiency (a late finding).

DIAGNOSIS

By definition, rhabdomyolysis is the breakdown of skeletal muscle cells with the subsequent release of intracellular contents. Assaying for elevated levels of these intracellular contents establishes the diagnosis.

Serum Creatine Kinase

Serum CK level is the most sensitive laboratory test for detecting rhabdomyolysis.[19] As muscle cells degrade and release CK into the plasma, the degree of CK

elevation correlates directly with the degree of muscle necrosis. Serum CK levels begin to rise 2 to 12 hours after muscle injury, peak at 1 to 3 days, and usually decline within 3 to 5 days after muscle injury ceases.[20] CK levels that remain persistently elevated are indicative of continued muscle injury, a compartment syndrome, or decreased renal clearance due to acute kidney injury.[2]

Rhabdomyolysis cannot be defined by a specific CK level. Most authorities would agree that a 5-fold or greater increase in serum CK is consistent with the diagnosis, although levels 40 times greater than normal may often be seen.[21] Early rhabdomyolysis should be suspected in at-risk patients with only a 2- to 3-fold increase in serum CK. Serial CK levels should be trended for progression in these patients.

Clinical context is also important to consider when evaluating CK levels, as higher levels do not always indicate a higher risk for complications. Young healthy athletes may have elevated CK levels as a normal consequence of muscle damage during vigorous physical exertion. These patients would not be expected to experience complications or progress to acute renal failure. However, elderly debilitated patients with lower elevations in total CK levels could progress to renal failure and therefore would represent a greater clinical concern. Such distinctions are important to make in terms of treatment decisions, expected complications, and prognosis. Contrast the case of an elderly woman with chronic kidney disease and a total CK level of 5000 IU/L with that of a young healthy marathon runner with a total CK level of 7000 IU/L after a race. This elderly patient requires aggressive management, including rehydration, bicarbonate infusion, and admission, whereas the marathon runner may only require oral rehydration in the emergency department followed by a repeat CK level several hours later.

Serum and Urine Myoglobin

Serum and urine myoglobin levels appear to be less sensitive tests for establishing the diagnosis of rhabdomyolysis. Myoglobin is a skeletal muscle protein involved in oxidative metabolism. Necrotic muscle cells release myoglobin, which is then excreted in the urine when the plasma concentration exceeds 1.5 mg/dL. Myoglobinuria causes the typical reddish-brown urine discoloration seen with rhabdomyolysis, clinically appreciable when urine myoglobin exceeds 100 mg/dL.[22] As myoglobin is a heme-containing compound, myoglobinuria will result in a positive urine dipstick for blood despite the absence of red blood cells on microscopic analysis.

Following muscle necrosis, myoglobinemia occurs before CK elevation does and subsequently is rapidly cleared via plasma metabolism and urinary excretion. This rapid clearance results in normal levels of myoglobin within 1 to 6 hours following onset of muscle injury. As such, serum and urine myoglobin levels may be only transiently abnormal in some cases of rhabdomyolysis and therefore should not be relied upon for a definitive diagnosis.

Other Diagnostic Studies

Other useful laboratory tests include measurement of serum electrolytes. Early in the course of illness, hyperkalemia, hyperphosphatemia, and hypocalcemia are seen frequently. Assessment of serum potassium levels is essential for averting malignant cardiac dysrhythmias in rhabdomyolysis-induced acute kidney injury. Measurement of urine electrolytes and creatinine allows for computation of fractional excretion of sodium, which may help differentiate AIRF caused by rhabdomyolysis (> 1%) from prerenal azotemia (< 1%). If concomitant DIC is present, thrombocytopenia, hypofibrinogenemia, prolonged bleeding times, and an elevated D-dimer level may be seen.

Finally, directed laboratory testing aimed at uncovering the precipitating cause of rhabdomyolysis is important. Diagnostic evaluations may include toxicologic testing, bacteriologic cultures, viral assays, and radiographic imaging. Genetic analysis, nerve testing, muscle biopsy, and the forearm ischemic test may be indicated in patients who are suspected of having an underlying genetic abnormality. The forearm ischemic test is performed as follows. Baseline urine myoglobin, venous lactate, CK, and ammonia levels are obtained at rest prior to testing. A sphygmomanometer cuff is then placed on the arm and inflated to 200 mm Hg to induce ischemia. The patient is instructed to repetitively grasp an object firmly in the hand for 2 to 3 minutes. The blood pressure cuff is then released and removed from the arm, and laboratory testing is repeated at 0, 5, 10, and 20 minutes. Elevation of lactate and ammonia to levels below what is normally expected during anaerobic metabolism is evidence of a pathway disturbance, and an enzyme deficiency is suggested.[23]

MANAGEMENT

Prevention of Complications

If patients present in extremis, attention should be given to basic airway, breathing, and circulatory measures (**Table 2**). On stabilization, prevention of the early and late complications of rhabdomyolysis becomes paramount in all patients. Management strategies should be tailored to clinical context, which considers risk of progression and complications. Variables such as the

inciting factor, patient age, patient comorbidities, and the presence of preexisting renal disease should be assessed when deciding upon the aggressiveness of therapy.

Volume resuscitation with isotonic crystalloid is the primary therapy for preventing rhabdomyolysis-induced renal injury. Increasing intravascular volume increases glomerular filtration rate (GFR), dilutes myoglobin and other nephrotoxins extruded during muscle injury, and improves overall oxygen delivery to ischemic tissue. Infusions of 10 to 15 mL/kg/hr of normal saline should be used initially, followed by hypotonic saline after initial resuscitation is completed.[24] Fluids should be titrated to an ideal urinary output of 2 mL/kg/hr.[25,26] Infusion should continue until adequate resuscitation has occurred and clinical and chemical evidence of myoglobinuria has disappeared (usually by the third day of hospitalization). Patients may require impressive amounts of fluid resuscitation to maintain adequate urinary output, as considerable fluid may be sequestered in injured muscles. For optimal outcomes, vigorous intravenous fluid rehydration should be started in the prehospital setting in crush injury patients at risk for developing rhabdomyolysis.[27] In patients with significant comorbidities such as heart failure, central venous pressure monitoring may be required to optimally assess the patient's volume status.

Additional measures are indicated to prevent acute kidney injury in patients at moderate to high risk of renal injury. Predictors for the development of acute kidney injury include preexisting renal disease, a peak CK level in excess of 6000 IU/L, dehydration (hematocrit > 50%, serum sodium level >150 mEq/L, orthostasis, pulmonary wedge pressure < 5 mm Hg, urinary fractional excretion of sodium < 1%), sepsis, hyperkalemia or hyperphosphatemia on admission, and the presence of hypoalbuminemia.[2] Two such preventive measures are urinary alkalinization with sodium bicarbonate and the use of the osmotic diuretic mannitol.

Dehydration and metabolic acidosis favor precipitation of myoglobin in renal tubules, enhancing and exacerbating its nephrotoxic effects. Urinary alkalinization is thought to enhance renal myoglobin clearance by increasing its solubility. Although large randomized trials are lacking, urinary alkalinization is recommended in patients with moderate to high risk of renal failure, preexisting renal disease, evidence of metabolic acidosis, or significant dehydration. The goal urine pH of 6.5 or higher can be obtained by adding 1 ampule of sodium bicarbonate (44 mEq) to 1 L of 50% normal saline or 2 to 3 ampules (88–132 mEq) to 1 L of 5% dextrose in water. This solution is then administered at a rate of 100 mL/hour. Of note, alkalinization can cause hypocalcemia and hypokalemia. Therefore, serial measurements of both serum electrolytes and urinary pH should be performed.

Mannitol is an osmotic diuretic commonly used to expand intravascular volume, promote renal vasodilation, and increase GFR in rhabdomyolysis patients. Mannitol increases urine flow, which may help prevent

Table 2. Managing Rhabdomyolysis

Prehospital care
If rhabdomyolysis is suspected, establish peripheral access and begin IV rehydration with normal saline
Initial hospital stabilization/treatment
Supportive care: ABC measures; treat associated life-threatening injuries
Confirm/establish diagnosis with history, physical examination, laboratory studies (eg, creatine kinase, creatinine, electrolytes, etc)
Rehydrate aggressively with normal saline at 10–15 mL/kg/hr to achieve urinary output of 2 mL/kg/hr; switch to hypotonic saline after resuscitation is complete
Continue rehydration for first 24–72 hr in moderate to severe cases or until patient is hemodynamically stable
In moderate to severe cases with risk of progression to acute renal failure, preexisting renal disease, or evidence of metabolic acidosis and dehydration, consider urinary alkalinization. The goal urine pH of ≥ 6.5 is achieved by adding 3 ampules of sodium bicarbonate to 1 L of 5% dextrose in water; the solution is infused at an initial rate of 100 mL/hr
In the nonoliguric patient, consider mannitol 1g/kg IV over 30 min, followed by 5 g/hr IV, for a total of 120 g/day; use mannitol to assist diuresis only in patients who have received adequate volume replacement
Monitor for and treat hyperkalemia aggressively
Monitor urinary output and renal function closely
Monitor for coagulopathy, compartment syndromes, and sepsis in severe cases
Consider hemodialysis in conjunction with a nephrologist for:
Fulminant renal failure with uremic encephalopathy
Uremic pericardial effusion with tamponade physiology
Refractory hyperkalemia, volume overload, or metabolic acidosis
Attempt to identify the inciting factor and stop further muscle damage and disease progression
Disposition
In mild to moderate cases with stable electrolytes that are responding to rehydration, admit to a general medicine ward
In patients with electrolyte abnormalities or underlying cardiac or renal disease, admit to a monitored bed
In severe cases, including those with fulminant renal failure with sequelae (pulmonary edema, symptomatic hyperkalemia, oliguria/anuria), persistent hypotension, or DIC, admit to intensive care unit

ABC = airway, breathing, circulation; DIC = disseminated intravascular coagulation; IV = intravenous.

obstruction from myoglobin-containing casts.[28] Mannitol also may draw fluid from the interstitial space, thus decreasing muscle edema in a concomitant compartment syndrome.[29] Mannitol is administered intravenously either as 1 g/kg over 30 minutes or as 25 g initially followed by 5 g/hr for a total of 120 g/day.[30] Mannitol should be given only after adequate volume resuscitation has occurred and should be avoided in cases of oliguria. Loop diuretics (eg, furosemide) have been used to enhance urinary output in some oliguric rhabdomyolysis patients.[31] However, they may acidify the urine and worsen myoglobin-induced toxicity. Therefore, loop diuretics should be avoided in patients who have not been adequately hydrated.

As mentioned previously, monitoring and treatment of electrolyte derangements in rhabdomyolysis patients is critical. Hyperkalemia is a life-threatening complication of rhabdomyolysis, causing cardiac instability and dysrhythmias. Conventional treatment for hyperkalemia (eg, calcium salts, sodium bicarbonate, glucose, insulin, albuterol, sodium polystyrene) should be employed. In the presence of profound hyperphosphatemia caused by muscle necrosis, calcium salts may be less effective, as the administered calcium may combine with the extracellular phosphate rapidly.[32]

Admission

All patients with rhabdomyolysis should be admitted for intravenous hydration, serial laboratory evaluation, and management of potential complications. Clinical context should determine level of admission. An unmonitored bed may be appropriate for healthy patients who respond to rehydration and have stable electrolyte levels. A monitored bed may be most appropriate for the first 24 to 48 hours, particularly in elderly patients, severely injured patients, and patients who have cardiac or renal comorbidities, as these patients tend to develop hyperkalemia and cardiac dysrhythmias. Placement in the intensive care unit is appropriate for patients who develop severe complications, such as acute kidney injury requiring dialysis, cardiac instability due to hyperkalemia, shock, and DIC.

In the appropriate setting, an otherwise healthy young patient, typically an athlete with a minimally elevated CK level, may be considered for outpatient management. These patients should be able to orally rehydrate, demonstrate a falling CK level on serial testing, and have stable electrolyte levels. Close primary care follow-up and detailed discharge instructions are important.

Management of Complications

Despite instituting preventive measures, acute kidney injury may develop in 30% to 40% of patients with rhabdomyolysis. Indications for emergent hemodialysis include hyperkalemia with evidence of cardiac instability, refractory metabolic acidosis, volume overload with pulmonary edema, uremic pericardial effusion with tamponade, and progressive renal failure with uremic encephalopathy. Early consultation with a nephrologist is recommended.

Early in rhabdomyolysis, hyperphosphatemia and hypocalcemia are seen as myocyte-released phosphate precipitates with calcium in injured muscle. Early treatment should be limited, as late hypercalcemia and hypophosphatemia will develop in most patients. Late hypercalcemia, more common with concomitant renal failure in advanced disease, may require volume expansion and diuretic therapy.

A compartment syndrome may cause or complicate rhabdomyolysis. Compartment syndrome occurs when the circulation to tissues within a closed space is compromised by increased pressure within that space.[33] This syndrome may develop either early or late in the clinical course of rhabdomyolysis, particularly in a traumatized limb due to crush injury. If compartment syndrome is suspected clinically and intracompartmental pressures exceed 35 mm Hg, emergent fasciotomy should be considered.[34]

As mentioned previously, DIC may be a life-threatening complication seen in rhabdomyolysis patients. DIC in this setting is usually worse during the third through fifth days after admission.[11] Serial laboratory measurements of coagulation times, platelet counts, and fibrinogen levels may be necessary. Life-threatening hemorrhage can occur, and it should be treated with fresh frozen plasma.

SUMMARY

The various etiologies and clinical presentations of rhabdomyolysis are diverse. With nontraumatic causes of rhabdomyolysis, the physician must maintain a high clinical suspicion in patients with predisposing factors. History and physical examination may be suggestive, but laboratory confirmation of elevated CK levels is essential in making the diagnosis. Management rests on the prevention and early identification of complications. Acute kidney injury may be averted through early and aggressive rehydration, alkalinization of the urine with sodium bicarbonate, and judicious use of mannitol. Life-threatening hyperkalemia, compartment syndromes, and DIC should be anticipated and treated immediately. With prompt recognition and aggressive treatment, the morbidity and mortality of rhabdomyolysis may be diminished. **HP**

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