

## Rhabdomyolysis: Advances In Diagnosis And Treatment

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### Abstract

Rhabdomyolysis is a potentially life-threatening condition caused by a breakdown of skeletal muscle and the release of the intracellular contents into the circulatory system. There are many possible causes, including crush injury, excessive muscular activity, medications, infections, and varied metabolic, connective tissue, rheumatologic, and endocrine disorders. It is vital that emergency clinicians consider the diagnosis when patients present with circumstances known to be high-risk for rhabdomyolysis, including intoxication, prolonged immobilization, and/or altered mentation. Optimal crystalloid selection is still debated, but immediate, aggressive intravenous volume expansion is indicated to prevent myoglobinuric renal failure. Serum potassium levels must be obtained and electrocardiograms must be evaluated to identify life- and limb-threatening complications of hyperkalemia. This review examines the current evidence on symptoms and diagnostic methods as well as standard first-line treatments of rhabdomyolysis. In addition, evidence from animal models on urine alkalinization with sodium bicarbonate infusion is discussed.

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### CME Objectives

Upon completion of this article, you should be able to:

1. Understand the importance of prompt recognition and treatment of rhabdomyolysis to mitigate risk of complications and increased morbidity.
2. Understand the challenges in diagnosis of rhabdomyolysis and overcome this barrier with increased awareness of the prevalence of the condition.
3. Discuss the controversies regarding fluid selection and urine alkalinization in the management of rhabdomyolysis.

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## Case Presentations

You receive an EMS notification for a patient with a potential “tib-fib” fracture. EMS reports a prolonged extrication of a night crew construction worker whose lower leg was trapped underneath a steel beam after a scaffolding collapse. EMS notes an obvious deformity to the mid-lower leg, with tense edema and bluish discoloration of the toes and delayed capillary refill. A large-bore IV was placed prior to extrication, and a rapid crystalloid infusion was initiated. Upon arrival, you note the absence of a dorsalis pedis pulse in addition to the tense edema of the lower leg and cyanotic digits. Your concern for compartment syndrome is confirmed with a Stryker needle registering a compartment pressure of 55 mm Hg. You notify the trauma surgeon of the need for fasciotomy and advise the OR. While this is happening, you get a call from the lab with a “panic value” of a CK level of 37,000 U/L, and the nurse reports gross blood output from the Foley catheter. His BUN is 28 and his creatinine is 4.

Shortly thereafter, a nurse informs you of a new patient who “just doesn’t look well.” You assess the patient, a 69-year-old woman who is coughing up green sputum, saturating 89% on room air, and is febrile, tachypneic, and tachycardic with a blood pressure of 86/40 mm Hg. The patient’s daughter informs you that her mother was just released from the hospital 6 days earlier after being treated for pneumonia. You suspect septic shock and instruct the nurse to place a nonrebreather mask on the patient. You administer broad-spectrum antibiotics, draw cultures and labs (including a venous lactate and a cardiac panel), and initiate a 30-cc/kg crystalloid infusion. The blood pressure normalizes, so you breathe a sigh of relief, but soon after, the lactate returns elevated at 8 mmol/L, which confirms your suspicion for severe sepsis. The nurse places a Foley catheter and reports that there is scant and “dark” urine in the bag. The WBC count returns at 18.4, and her BUN and Cr are 32 and 5.5, respectively. You note that the BUN:Cr ratio is odd, considering her previously normal renal function; you expected an increased ratio due to prerenal azotemia from severe sepsis. You then notice that the CK level is 67,000 U/L with normal MB fraction. To confirm your hunch, you check the UA, which returns positive for “blood” but does not show any red blood cells in the sediment.

These 2 cases remind you that rhabdomyolysis has many causes, but the treatment in all cases is based on an aggressive hydration strategy. You recall that sodium bicarbonate infusion may be indicated and wonder: when, how, and to whom should it be initiated? You also wonder, “Is there anything else I can do for these patients that would mitigate against complications from renal failure?”

## Introduction

Rhabdomyolysis is a potentially life-threatening condition characterized by the breakdown of skeletal muscle and the release of intracellular contents into the circulatory system. Although generally

the consequence of a primary pathophysiological process, there are many different causes and varied presentations of rhabdomyolysis. The diagnosis of rhabdomyolysis can be easily overlooked when the primary process—such as compartment syndrome or sepsis—demands immediate action. Experienced emergency clinicians excel at quickly and efficiently constructing a broad differential diagnosis, rapidly identifying conditions with greatest risk to life, and taking critical actions as needed for the presumptive diagnosis. This is often done subconsciously, without the benefit of a complete data set, and with great accuracy; however, over-reliance on the heuristics that distinguish the specialty can lead to premature diagnostic closure once a diagnosis is identified, which makes missing additional diagnoses like rhabdomyolysis all the more precarious.

The cause of rhabdomyolysis may be evident from the patient’s history or from the immediate circumstances preceding the disorder; however, in a great number of cases, a precipitant is not immediately obvious. Nearly every class of drugs and medications has been reported to cause rhabdomyolysis, thus highlighting the risk of underdiagnosis. In this issue of *Emergency Medicine Practice*, the various causes of rhabdomyolysis are reviewed. The most recent literature on the pathophysiology, diagnosis, and management is analyzed, and best practice recommendations are made with the hope of mitigating the risk of missing this diagnosis and maximizing outcomes.

## Critical Appraisal Of The Literature

A literature search of the PubMed database for *rhabdomyolysis* was performed, including reviews, case series, case reports, and prospective randomized trials. More than 210 articles were reviewed, and additional references were identified from the bibliographies.

A search of the National Guidelines Clearinghouse produced only 1 practice guideline (based on 2 studies already identified in the PubMed search). A search of the Cochrane Database of Systematic Reviews failed to produce any reviews on the topic, although a review is currently underway to assess the safety and efficacy of renal replacement therapy for rhabdomyolysis.

The literature is replete with case reports of the many causes of rhabdomyolysis. Much of the pathophysiology was elucidated from autopsies on casualties of World War II as well as from animal studies. Management recommendations come from retrospective reviews, animal data, and a very limited number of prospective trials. Recommendations made in this review are evidence-based, when available. Recommendations made based on accepted practice or expert consensus are explicitly noted.

## Etiology And Pathophysiology

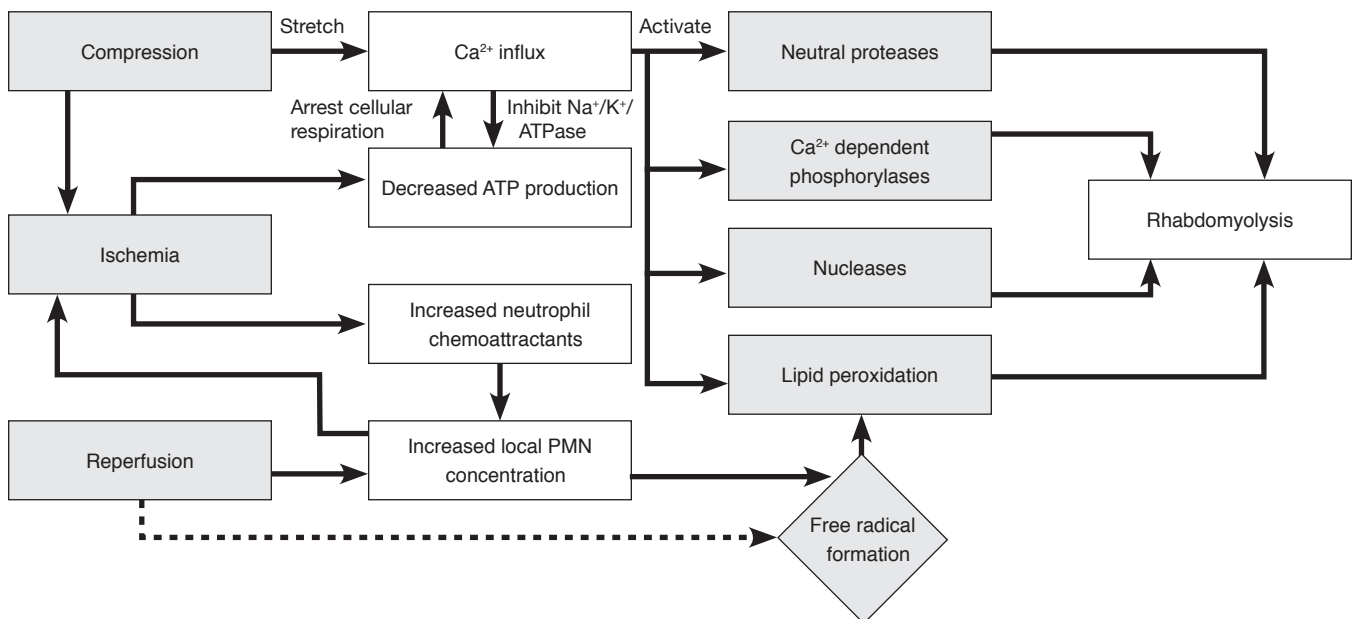
Skeletal muscle comprises 42% of body mass<sup>1</sup> and requires a large amount of adenosine triphosphate (ATP), even at rest. During extremes of physical activity, skeletal muscle can consume up to 85% of the total body requirement of oxygen to produce enough ATP to function properly. Myoglobin binds and delivers oxygen to active skeletal muscle in a pH-independent fashion, giving it a higher affinity for oxygen than hemoglobin. This ensures its ability to extract oxygen from the circulation and deliver it to muscle cell mitochondria, even in times of low partial pressures of oxygen.

ATP is the essential ingredient for a properly functioning muscle cell membrane, known as the *sarcolemma*. A series of sarcolemma ion pumps require ATP for proper maintenance of electrochemical gradients. For instance, the sodium ( $\text{Na}^+$ )/potassium ( $\text{K}^+$ )/ATPase ( $\text{Na}^+/\text{K}^+$ /ATPase) actively transports 3  $\text{Na}^+$  out of the cell in exchange for every 2  $\text{K}^+$  transported intracellularly in order to maintain a negative membrane potential. This negative potential draws  $\text{Na}^+$  intracellularly, in exchange for calcium ( $\text{Ca}^{2+}$ ) via a  $\text{Na}^+/\text{Ca}^{2+}$  exchanger, required for maintenance of very low intracellular  $\text{Ca}^{2+}$  concentrations.  $\text{Ca}^{2+}$ /ATPase pumps in the sarcoplasmic reticulum and mitochondria also aid in keeping cytoplasm  $\text{Ca}^{2+}$  concentrations low. Tightly regulated calcium homeostasis is essential for the function of the muscle cell.

Any process that disrupts a myocyte from maintaining a calcium gradient homeostasis will lead to breakdown of the cell. There are 2 primary pathologic mechanisms by which calcium accumulates in the cell: (1) direct cell membrane damage, and (2) ATP depletion. Cell membrane damage, whether from traumatic, hereditary, or biochemical factors, directly leads to  $\text{Ca}^{2+}$  influx. ATP depletion, on the other hand, leads to increased intracellular  $\text{Ca}^{2+}$  concentrations in a more indirect fashion. ATP depletion disrupts proper functioning of the  $\text{Na}^+/\text{K}^+$ /ATPase, causing an increase in intracellular  $\text{Na}^+$  concentrations, which results in increased  $\text{Na}^+/\text{Ca}^{2+}$  ion exchanger function (also ATP-dependent) and increased cytosolic calcium concentrations. This temporary hyperactivity of the ATP-dependent  $\text{Na}^+/\text{Ca}^{2+}$  ion exchanger further depletes the cell of ATP and its ability to maintain low calcium concentrations. Once ATP debt reaches critical levels, the cell's ability to keep calcium out and maintain the appropriate membrane potential for proper functioning is compromised. (See Figure 1.)

Several events take place when cytosolic calcium exceeds a safe threshold for the cell. First, the mitochondria—which serve as a safety net buffer for excess cytosolic calcium—become overwhelmed. With this, oxidative phosphorylation is disrupted, ATP production suffers, and ATP debt deteriorates. Even more importantly, apoptosis is triggered. Mitochondrial production of reactive oxygen species increases, leading to free radical disruption of cell and organelle membranes. Cytosolic calcium also

**Figure 1. Pathophysiology Of Rhabdomyolysis**



Abbreviations: ATP, adenosine triphosphate;  $\text{Ca}^{2+}$ , calcium;  $\text{K}^+$ , potassium;  $\text{Na}^+$ , sodium; PMN, polymorphonuclear neutrophil.

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pathologically activates a series of proteases and phospholipases, damaging the myofibrillar network. Once the sarcoplasmic reticulum and mitochondria are made dysfunctional by free radicals and degradative enzymes, their stores of calcium are released into the cytosol, further injuring the cell as it spirals towards cell death.

## Differential Diagnosis

The causes of rhabdomyolysis are extensive and are summarized in **Table 1**. As mentioned previously, any process that results in ATP depletion and/or membrane damage can lead to rhabdomyolysis. When differentiating among known causes of the disorder, consider whether: (1) any process has occurred that impairs the muscle's ability to produce or utilize ATP; (2) there has been any disruption in the delivery of oxygen, glucose, or other nutrients to skeletal muscle; (3) the metabolic demands of the skeletal muscle have increased beyond the ability of the organism to deliver oxygen and nutrients; or (4) there has been direct myocytic damage.

## Prehospital Care

The goals of prehospital management include rapid recognition of the potential for development of rhabdomyolysis. With the exception of certain circumstances such as limb ischemia from presumed vascular etiologies (ie, embolic limb ischemia), nontraumatic causes of rhabdomyolysis are much more difficult to identify in the prehospital environment. Nonetheless, awareness of highly associated risk factors such as drug or alcohol intoxication or prolonged immobilization may tip off the first responder to the potential for rhabdomyolysis. More important than precise diagnosis is providing these circumstantial details to the emergency clinician, especially when the patient's mental status precludes the ability to obtain history. Consideration of the diagnosis in the trauma patient may prove beneficial, such as with victims of building collapse or direct extremity trauma with significant swelling, since immediate intravenous (IV) fluid resuscitation may prevent the development of myoglobinuric renal failure.<sup>2,3</sup>

## Emergency Department Evaluation

Patients with rhabdomyolysis will differ widely in the severity of their presentation, ranging from subclinical to life-threatening, and it can be obvious or found incidentally on laboratory analysis. No single historical or physical examination finding can reliably diagnose or rule out rhabdomyolysis. In fact, most of the largest series to date describe alcohol and illicit drug intoxication as the most commonly

associated etiological factors, thereby rendering the acquisition and verification of history even more difficult.<sup>4-8</sup> The key to the emergency department (ED) evaluation, therefore, is for the provider to consider the diagnosis when patients present with high-risk circumstances known to be associated with rhabdomyolysis, eg, altered mentation, intoxication, and/or prolonged immobilization. History by first responders or witnesses can be helpful to describe the scene when history is otherwise unavailable.

## History

The classic presentation of rhabdomyolysis includes localizing myalgias, muscle stiffness, cramping, swelling, tenderness, and tea-colored urine. The thighs, calves, and lower back are most commonly affected<sup>9</sup>; however, the classic presentation is not the most common one. In fact, one of the largest prospective observational series to date shows that 50% of patients did not report myalgias or muscle weakness despite serologically proven rhabdomyolysis.<sup>9</sup> In a smaller study by Grossman et al, 60% of patients described pain referable to the musculoskeletal system, though it was noted that the complaints in one-third of these patients were so mild that they were only recalled retrospectively once myoglobinuria was confirmed.<sup>7</sup> Complaints of urine that is darker than normal in the appropriate clinical setting should not be dismissed. Although this may be due to dehydration, a simple urine dipstick and urinalysis can help distinguish dehydration from myoglobinuria. Nonspecific constitutional symptoms such as malaise, subjective fevers, nausea, and vomiting have been reported (particularly in severe cases), but it may be difficult to distinguish these from a causative syndrome.

## Physical Examination

Similar to a patient's history, no single individual sign on physical examination can diagnose or exclude the diagnosis of rhabdomyolysis. Examination findings may be subtle and easily missed if clinical suspicion is lacking, though traumatic rhabdomyolysis tends to manifest with more obvious signs of muscle damage. In one series, extremity swelling was present at initial evaluation in 52% of patients.<sup>8</sup> In a much larger series, muscle swelling was present in only 5% of patients.<sup>9</sup> Both groups were a heterogeneous population, often with multiple potential causes for rhabdomyolysis (eg, alcohol intoxication plus direct extremity trauma). The absence of muscle swelling may be explained by the fact that many patients who develop rhabdomyolysis are profoundly dehydrated, and in these cases, extremity swelling may not be evident until after IV fluid resuscitation. This was demonstrated in the study by Gabow et al when these precise physical examination findings were observed for and manifested

at some later point in their hospitalization.<sup>9</sup> Other small series highlight the inadequacy of physical examination alone. Grossman et al described a full 33% of patients with serologically confirmed rhabdomyolysis without any abnormal physical examination findings whatsoever. Those who did have findings exhibited 1 or more of the following findings: extremity swelling, tenderness, motor weakness, sensory deficits, and pain with passive range of motion.<sup>7</sup> What makes the study by Grossman et al even more salient is that their evaluation spanned the initial 48 hours of hospitalization, and not just an isolated physical examination at presentation. That said, the aforementioned findings tend to be more evident when muscle damage is severe enough to progress to compartment syndrome. Overlying skin changes may be present, particularly in cases of limb ischemia or compression necrosis.<sup>8</sup>

## Diagnostic Testing

A diagnosis of rhabdomyolysis is made by serological testing, namely serum creatine phosphokinase (CK) levels. The consensus definition has rather arbitrarily been chosen as 5 times the upper limit of normal, or approximately 1000 U/L. This confounds some of the earlier literature which used levels of 500 U/L as a diagnostic cutoff, though this may only pertain to diagnosis, since complications at levels between 500-1000 U/L are unlikely.

## Laboratory Tests

### Creatine Phosphokinase

CK is an intracellular enzyme that functions as an energy reservoir for ATP. The serum concentration of CK typically rises in the first 12 hours after injury, peaks at 3 days, and normalizes at around 5 days.

**Table 1. Differential Of The Causes Of Rhabdomyolysis**

Cause	Pathophysiology
Prolonged immobilization	Coma (from any cause), prolonged general anesthesia
Excessive muscular activity	Seizures, alcohol withdrawal syndrome, strenuous exercise, tetanus, severe dystonia, acute mania
Muscle ischemia	Thromboembolism, external compression, carbon monoxide poisoning, sickle cell disease
Temperature extremes	Heat stroke, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, hypothermia/frostbite
Electrical current	Lightning strike, high-voltage injury, electrical cardioversion
Electrolyte abnormalities	Hypokalemia (licorice ingestion, diarrhea, diuretics, primary hypoaldosteronism) hypophosphatemia, hyponatremia, hypernatremia
Toxins and recreational drugs	Ethanol, methanol, ethylene glycol, heroin, methadone, barbiturates, cocaine, caffeine, amphetamine, LSD, MDMA (ecstasy), mushrooms, PCP, benzodiazepines, toluene, etc.
Trauma	Crush syndrome, compartment syndrome
Medications	Antihistamines, salicylates, neuroleptics (neuroleptic malignant syndrome), cyclic antidepressants and selective-serotonin reuptake inhibitors (via serotonin syndrome), anticholinergics, laxatives (likely via electrolyte abnormalities), anesthetics and paralytic agents (especially succinylcholine), quinine, corticosteroids, theophylline, aminocaproic acid, propofol, colchicine, antiretrovirals, etc.
Infections	Bacteria: <i>Escherichia coli</i> , <i>Shigella</i> , <i>Salmonella</i> , <i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , Group A <i>Streptococcus</i> , <i>Clostridium</i> , etc. Viruses: Influenza A and B, cytomegalovirus, herpes simplex virus, Epstein-Barr virus, HIV, coxsackievirus, West Nile virus, varicella-zoster virus
Metabolic myopathies	Inherited disorders manifest with enzyme deficiencies in carbohydrate and lipid metabolism or myopathies
Connective tissue disorders	Polymyositis, dermatomyositis, Sjögren syndrome
Rheumatological disorders	Systemic lupus erythematosus
Endocrine disorders	Hypothyroidism, thyroid storm
Biological toxins	Snakebite, bee envenomation, scorpion sting, spider bite
Other/unknown	Cardiac arrest, cardiopulmonary resuscitation

Causes and pathophysiologies are the most commonly reported; list is not exhaustive

Abbreviations: HIV, human immunodeficiency virus; LSD, lysergic acid diethylamide; MDMA, methylenedioxymethamphetamine; PCP, phencyclidine.

The degree of elevation of CK correlates with the degree of muscle injury,<sup>10</sup> but it is not a sensitive predictor for the development of acute myoglobinuric renal failure.<sup>11</sup>

### Myoglobin

Myoglobin is a low-molecular-weight protein with a heme moiety whose function is to extract oxygen from the circulation and supply it to active skeletal and cardiac muscle. The first descriptions of rhabdomyolysis identified, post mortem, myoglobin casts in the kidneys of World War II victims of crush injuries,<sup>12</sup> thus rendering the presence of abnormally elevated myoglobin levels in the serum or urine as pathognomonic for rhabdomyolysis. Myoglobin is released rapidly from damaged muscle. The level peaks at 8 to 12 hours and is completely removed from the serum within 24 hours.<sup>13</sup> (See Figure 2.) Myoglobin has a half-life of 1 to 3 hours, making serum diagnosis unreliable. Similarly, urine myoglobin levels are contingent upon the degree of muscle injury, urinary flow rate, and volume status of the patient, making the presence of urine myoglobin an insensitive marker of disease presence. Myoglobin is likely to be present early in the course of disease; however, its sensitivity as a diagnostic test for rhabdomyolysis is correlated with time from insult. Ellinas et al found that only 50% of patients in their series had urine positive for myoglobin despite a mean CK level of approximately 15,000 U/L.<sup>14</sup>

### Urine Dipstick And Urinalysis

Myoglobinuria will be detected by urine dipstick as positive for blood. The drawback of this test is its inability to distinguish between heme compounds. Microscopic analysis will, however, show few, if any, red blood cells, thereby distinguishing between hemoglobin/hemoglobin-rich red blood cells (from hemolysis or hematuria) and myoglobin. In combination with elevated plasma CK level, myoglobinuria from rhabdomyolysis will be confirmatory. At plasma concentrations > 100 to 300 mg/L, macroscopic myoglobinuria will manifest as tea-colored urine.

An acidic urine pH plays a role in myoglobin cast and uric acid crystal formation as well as pathological myoglobin metabolism in tubular epithelial cells. Proteinuria is demonstrated in up to 45% of cases due to the detection of the globin component of myoglobin.<sup>13</sup> Urine sediment analysis will show myoglobin casts and dead epithelial cells; however, the absence of urine myoglobin is inadequate to rule out rhabdomyolysis. In one of the largest and most recent retrospective reviews, Melli et al found urine testing to be positive in only 19% of cases.<sup>15</sup>

### Basic Metabolic Panel

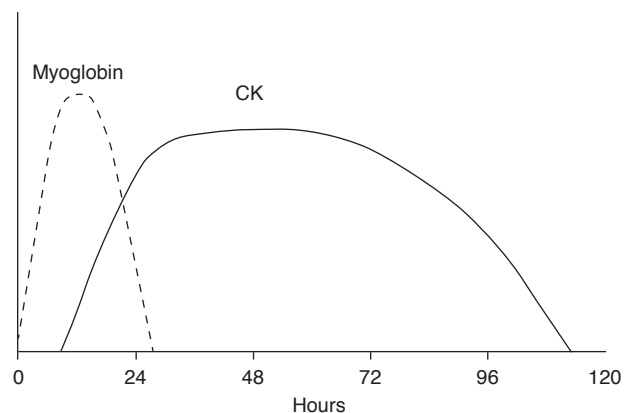
A number of electrolyte abnormalities are associated with rhabdomyolysis, but none are specific

enough for diagnostic certainty in and of themselves. A combination of findings will lend credence to a diagnosis of rhabdomyolysis, but any abnormalities need to be interpreted in the context of potential muscle injury and the diagnostic-standard CK level. Hyperkalemia, hyperphosphatemia, and early hypocalcemia followed by late hypercalcemia are common electrolyte disturbances. Hyperkalemia's potentially lethal effects on cardiac conduction can be exacerbated by metabolic acidosis from organic acid production in the form of lactate or uric acid from muscle cell breakdown.

When liberated phosphate from damaged muscle reaches critical levels in the serum, calcium-phosphate crystals form and deposit at the site of damaged muscle. Exogenous calcium, when given therapeutically to address early hypocalcemia, also deposits in rhabdomyolysed muscle. This can be visualized radiographically.<sup>16</sup> (See Figure 3.)

The BUN and creatinine both increase but with a characteristic decrease in the BUN:Cr ratio. This is due to large amounts of creatinine released into the serum from damaged muscle. A normal BUN:Cr is 10:1, while in rhabdomyolysis it can be as low as 5:1 or even less.

**Figure 2. Variations Of Myoglobin And Creatine Phosphokinase During Rhabdomyolysis**



Myoglobin is the first enzyme that increases, but, due to its rapid clearance from the plasma, it returns to normal levels within the first 24 hours after the onset of symptoms. CK increases a few hours later than myoglobin, reaches its peak value within the first 24 hours, and remains at these levels for 3 days. CK is considered to be a more useful marker for the diagnosis and assessment of the severity of muscular injury due to its delayed clearance from the plasma.

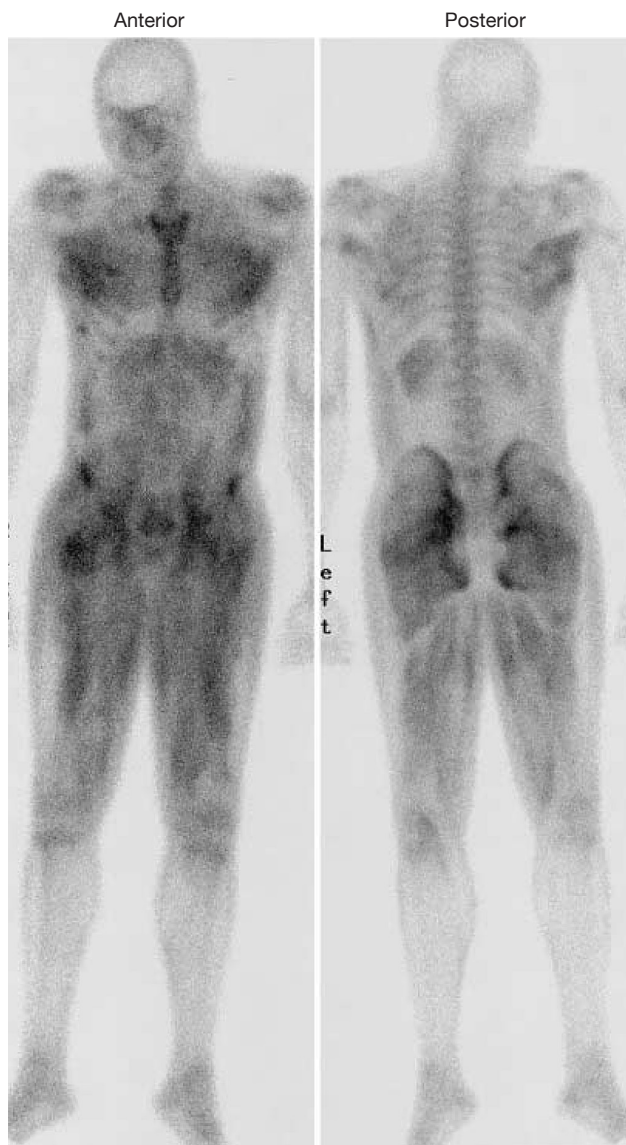
Abbreviation: CK, creatine phosphokinase.

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### Liver Function Tests Panel

While not routinely indicated, a liver function tests (LFT) panel may provide prognostic information. Hypoalbuminemia is a poor prognostic sign in rhabdomyolysis, as this represents capillary rupture with leakage of albumin at the site of damaged muscle tissue. Though not evidence-based, this test may be considered by the treating clinician in cases of severe rhabdomyolysis.

**Figure 3. Technetium Bone Scan In A Patient With Rhabdomyolysis**



This technetium (Tc) bone scan in a patient with rhabdomyolysis shows uptake of the radioisotope, which is a calcium analog, into rhabdomyolysed muscle, especially in buttock and thigh.

With kind permission from Springer Science+Business Media: *Intensive Care Medicine*. Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. Volume 27, issue 5. Page 804. S. Holt. Figure 2.

### Complete Blood Count

A complete blood count (CBC) is not specifically indicated for the diagnosis of rhabdomyolysis, but some prognostic information can be gleaned from it. Red blood cells can pathologically accumulate in the interstitium when capillary rupture ensues, just as plasma volume can accumulate at the site of damaged muscle. This contributes to hypovolemic and hemorrhagic shock. As in all cases of new anemia, other sources of acute hemorrhage must be excluded.

### Coagulation Panel/D-dimer/Fibrinogen

In rare and severe cases, coagulation disorders such as disseminated intravascular coagulopathy can ensue, triggered by released thromboplastin from damaged tissue. Again, this test serves a prognostic, not diagnostic, function.

### Electrocardiogram

The utility of an electrocardiogram (ECG) to assist in the evaluation and management of patients with rhabdomyolysis is limited to its ability to suggest hyperkalemia. As mentioned previously, significant muscle injury may lead to a rise in serum  $K^+$ . Hyperkalemia leads to cardiac dysrhythmias, especially in rhabdomyolysis when serum  $Ca^{2+}$  tends to be low and metabolic acidosis is present. The ECG is not sensitive in predicting hyperkalemia. In fact, there is evidence that, occasionally, even severe hyperkalemia is not associated with ECG manifestations.<sup>17</sup> While not sensitive as a screening tool, ECG provides a useful adjunct, as it may demonstrate cardiac effects more rapidly and reliably than serum testing.

### Complications Of Rhabdomyolysis

Rhabdomyolysis increases morbidity or mortality, as muscle breakdown results in other complications. These are classified temporally into early and late complications.

#### Early Complications

##### Compartment Syndrome

A massive influx of calcium and sodium leads to the accumulation of large amounts of extracellular fluid in the muscle cells, causing local edema and raised intracompartmental pressures that can inhibit perfusion and lead to increased muscle ischemia. Prolonged ischemia and infarction of muscle tissue can lead to replacement of muscle tissue with inelastic, fibrous tissue, resulting in severe contractures (Volkmann contracture).

##### Electrolyte Disorders And Acidosis

Because 98% of total body potassium is stored intracellularly, damage to as little as 100 grams of muscle tissue can raise serum potassium by 1.0 mEq/L. This

can lead to potentially fatal dysrhythmias, particularly when complicated by metabolic acidosis (from release of organic ions such as lactate and sulfate from damaged tissue) and/or hypocalcemia (from deposition in necrotic muscle tissue with released intracellular phosphate). Early-phase hypocalcemia is typically followed by late-phase hypercalcemia, as calcium phosphate crystals become mobilized and re-enter the circulation. Therefore, it is not advisable to treat hypocalcemia unless dangerous hyperkalemia or severe symptoms (ie, tetany) are present.

### Hypovolemia

Fluid sequestration by damaged muscle leads to profound intravascular volume depletion. This shift may exceed 15 liters and exacerbates the potential for acute renal failure.

### Hepatic Dysfunction

Large elevations in liver enzymes may occur in the acute phase of rhabdomyolysis. The significance of these elevations is not known, but they tend to normalize upon resolution of rhabdomyolysis.<sup>18</sup>

### Late Complications

#### Myoglobin-Induced Acute Kidney Injury

Experimental studies, mostly in rats, suggest that there are 3 pathogenetic factors involved in rhabdomyolysis-induced acute renal failure: (1) myoglobin cast formation in the distal convoluted tubules, (2) direct cytotoxic action of myoglobin on the epithelial cells of the proximal convoluted tubules, and (3) intrarenal vasoconstriction and ischemia.<sup>19</sup>

Myoglobin seems to have no marked nephrotoxic effect in the tubules unless the urine is acidic. Initial theories held that myoglobin casts themselves were responsible for decreased urinary flow, but there is evidence suggesting that casts are symptomatic of poor urinary flow and not the causative agent.<sup>20</sup> This would suggest that poor washout of casts is the issue, not tubular obstruction per se.

It is more likely that free radical production from reduction-oxidation (redox) reactions of myoglobin occurring in the proximal tubular cells (see Figure 4), in combination with renal vasoconstriction (from hypovolemia-induced upregulation of the renin-angiotensin neuroendocrine system), is responsible for the bulk of kidney injury, particularly in the presence of acidic urine.

#### Disseminated Intravascular Coagulation

On rare occasions, thromboplastin, a prothrombotic agent, can be released from damaged muscle in amounts significant enough to cause a consumptive coagulopathy.

## Treatment

The mainstays of management of rhabdomyolysis are focused on treating the cause, preventing renal failure, and managing life- or limb-threatening complications.

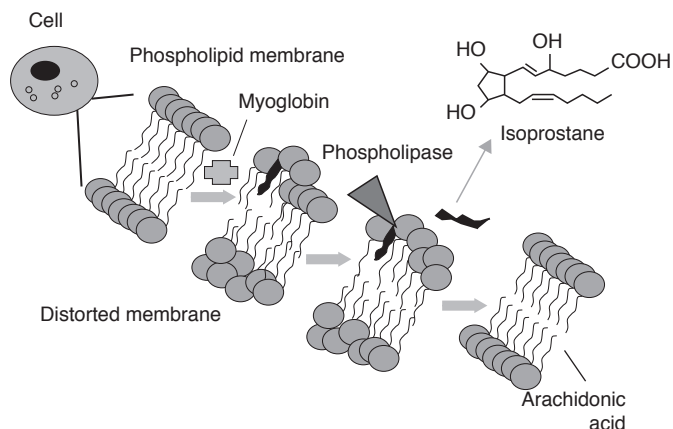
### Fluid Resuscitation

Aggressive volume expansion is critical in avoiding myoglobin-induced acute renal failure. Multiple case series in the literature report that intravascular volume depletion is associated with the development of acute renal failure. In a prospective case series, Ron et al described 7 patients who were victims of a building collapse and who presented with crush injury with rhabdomyolysis.<sup>3</sup> They reported that the patients who went on to develop acute renal failure had a longer delay to fluid resuscitative therapy than those who did not develop renal failure. Reis et al also reported markedly increased rates of renal failure in a series of patients who were trapped under rubble with more than 12 hours elapsed from extrication to initiation of resuscitation versus those who were rescued and treated more rapidly.<sup>21</sup> For victims of mass casualty events with prolonged extrication times, initiation of fluid resuscitation is recommended even before complete extrication.<sup>3,22</sup>

### Fluid Selection And Urine Alkalinization

While the need for early, aggressive volume expansion is universally accepted, the fluid composition is more controversial, especially regarding the concept

**Figure 4. Synthesis And Cleavage Of Isoprostanes In Plasma Membranes**



Free radical attack on arachidonic acid forms an isoprostane esterified to membrane phospholipid, and this perturbs the membrane structure. Phospholipase cleavage restores membrane integrity and releases free isoprostane.

With kind permission from Springer Science+Business Media: *Intensive Care Medicine*. Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. Volume 27, issue 5. Page 807. S. Holt. Figure 4.



of urine alkalinization. The principles of urine alkalinization are derived empirically from animal data and include the facts that: (1) myoglobin precipitation is increased in acidic urine; (2) redox cycling of myoglobin and lipid peroxidation, and thus tubule injury, are inhibited by alkaline urine<sup>23,24</sup>; and (3) animal models demonstrated that myoglobin only induces renal vasoconstriction in an acidic medium.<sup>25</sup> Myoglobin-induced lipid peroxidation occurs at concentrations much lower than those that lead to precipitation of casts in the distal tubules. The discovery that urine alkalinization inhibits redox cycling of myoglobin and lipid peroxidation lends further credence to its therapeutic utility.<sup>24</sup>

In clinical studies, however, urine alkalinization has not been shown to impact outcomes. Gleaning useful information from these studies is difficult, and the results should be interpreted with caution. The relatively few studies are limited by small sample sizes, variation in the severity of rhabdomyolysis, and confounding effects of multiple therapeutic measures. For instance, a study by Homsy et al was retrospective and compared saline-only fluid resuscitation to a saline-bicarbonate-mannitol therapeutic approach.<sup>26</sup> While the authors concluded that there were no differences in mortality between the 2 groups, the study was not designed to parse out the individual effects of bicarbonate versus mannitol, compared to saline. The saline group had lower overall CK levels (approximately 1700 U/L) compared to the saline-bicarbonate-mannitol group (approximately 3300 U/L).<sup>26</sup> Perhaps most important is the fact that major complications of rhabdomyolysis—namely, myoglobinuric renal failure—are highly unlikely when peak levels of CK remain < 5000 U/L,<sup>27</sup> so the lack of treatment effect is not particularly reassuring.

Brown et al performed a study that was also limited by the confounding effects of multiple therapeutic interventions (bicarbonate plus mannitol vs saline only) as well as its retrospective nature, but it also showed no difference in mortality, rates of acute renal failure, and need for dialysis in patients with CK levels > 5000 U/L.<sup>27</sup>

To date, the only prospective randomized trial is by Cho et al, comparing fluid regimens in 28 patients with doxylamine-induced rhabdomyolysis<sup>28</sup>; however, its results are limited by the end points evaluated. Patients were randomized to receive lactated Ringer (LR) versus normal saline, both given at 400 mL/hr for 12 hours. The authors tracked urine pH and serum electrolytes as well as peak and time to normalization of CK levels. There were no cases of acute renal failure in either group, so conclusions cannot be made regarding fluid type. One important result of their study was that significantly more bicarbonate was needed in the normal saline group to optimize urine pH levels (pH > 6.5). This is almost

certainly due to the hyperchloremic metabolic acidosis induced by large-volume normal saline resuscitation.<sup>29</sup> On the other hand, LR has a mild alkalinizing effect in the serum.

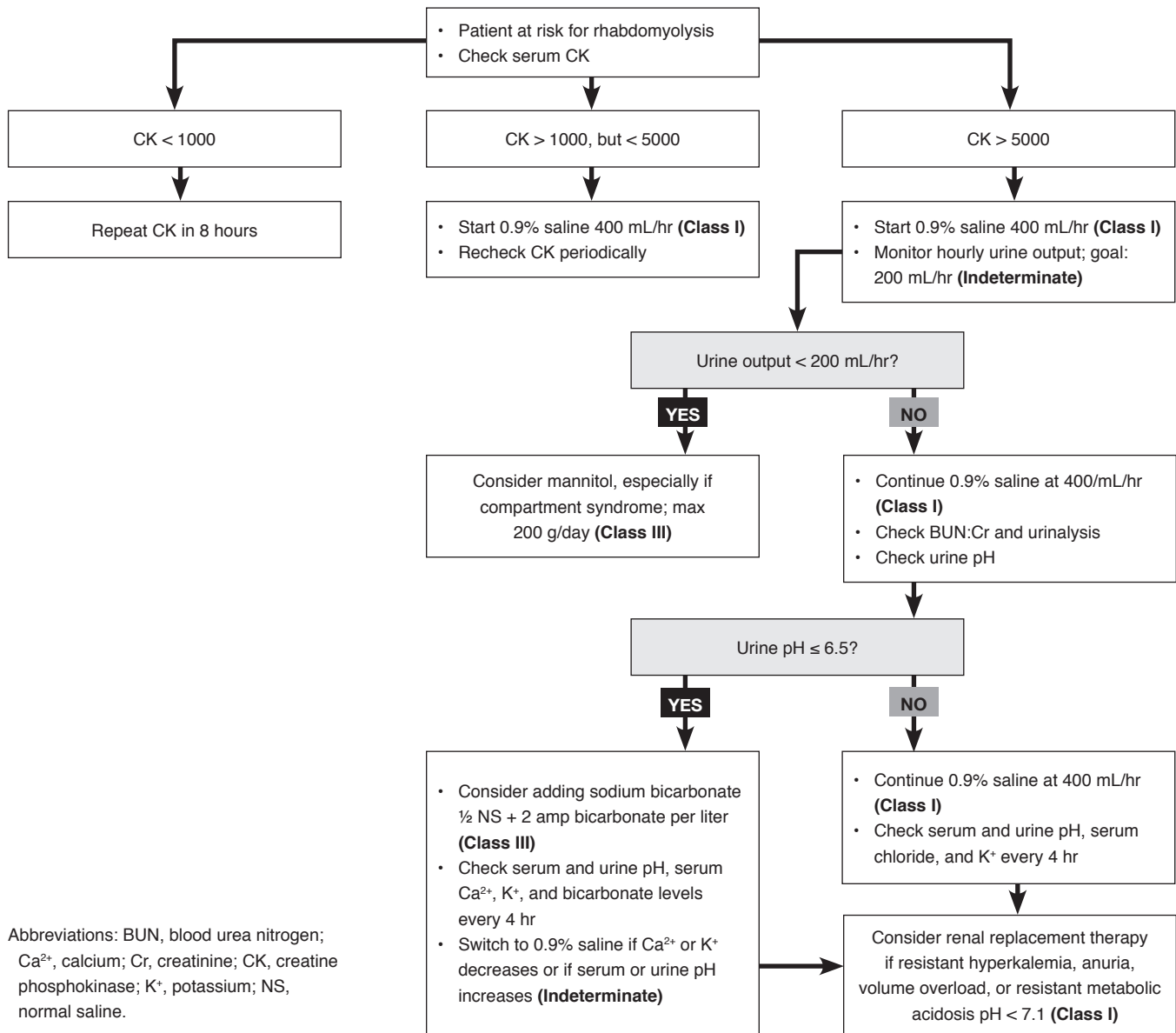
The precise benefits of urine alkalinization remain unclear with regard to patient-oriented outcomes (acute renal failure, mortality). That said, the abundance of animal data associating acidic urine with deleterious effects of myoglobin, in combination with the known acidifying effects of normal saline, guide a two-fold fluid resuscitation strategy. The administration of both normal saline and sodium bicarbonate seems to be a reasonable approach, especially in patients with metabolic acidosis. If sodium bicarbonate therapy is used, the urine and serum pH, serum bicarbonate, potassium, and calcium levels must be monitored. The urine should be alkalinized to a pH > 6.5 and serum pH 7.40-7.45. Bicarbonate therapy should be discontinued in favor of normal saline if calcium levels become dangerously low (total corrected Ca<sup>2+</sup> < 9 mg/dL or ionized Ca<sup>2+</sup> < 4.5 mg/dL) or if no improvement in urine pH is noted after 4 to 6 hours. If a saline-only approach is used, serum chloride and pH levels should be monitored and the saline discontinued if a (hyperchloremic) metabolic acidosis is induced iatrogenically. In this instance, a less-acidifying solution (ie, LR or bicarbonate) can be used. The evidence for this approach is lacking, but it seems reasonable given current experimental and clinical knowledge. While precise guidelines do not exist, widespread practice suggests that fluids should be administered with a goal urine output of 3 mL/kg/hr (approximately 200 mL/hr)<sup>30</sup> until CK levels decrease to 1000 U/L<sup>31</sup> or myoglobinuria is cleared.<sup>25</sup> The approach to evaluating and managing patients with rhabdomyolysis is summarized in **Table 2 (see page 11)**.

## Diuretics

### Mannitol

The use of mannitol remains controversial. The addition of mannitol has not been shown to be more beneficial than fluid expansion alone in human studies,<sup>26</sup> though precise knowledge of its effects are limited by poor study design. Mannitol has numerous theoretical benefits, including osmotic diuresis, urinary dilution of myoglobin, ability to relieve compartment pressures, and free-radical scavenging. Animal studies suggest that the beneficial effects of mannitol are primarily due to its function as an osmotic diuretic.<sup>32</sup> On the other hand, large accumulated doses of mannitol have the potential to lead to a condition known as “osmotic nephrosis,” which is manifested by renal vasoconstriction and tubular toxicity.<sup>32,33</sup> Based on current evidence, the use of mannitol in rhabdomyolysis should be limited to cases of compartment syndrome complicated by rhabdomyolysis.<sup>9</sup>

# Clinical Pathway For Rhabdomyolysis



Abbreviations: BUN, blood urea nitrogen; Ca<sup>2+</sup>, calcium; Cr, creatinine; CK, creatine phosphokinase; K<sup>+</sup>, potassium; NS, normal saline.

## Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

### Class I

- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

#### Level of Evidence:

- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

### Class II

- Safe, acceptable
- Probably useful

#### Level of Evidence:

- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

### Class III

- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

#### Level of Evidence:

- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

### Indeterminate

- Continuing area of research
- No recommendations until further research

#### Level of Evidence:

- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and represen-

tatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA*. 1992;268(16):2289-2295.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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## Furosemide

Loop diuretics also increase urinary flow but have the disadvantage of acidifying urine,<sup>34</sup> and no study to date has shown a clear benefit in patients with rhabdomyolysis.<sup>35,36</sup> Therefore, they are not recommended as prophylaxis against myoglobin-induced renal failure. Additionally, furosemide may worsen hypocalcemia in the setting of rhabdomyolysis.<sup>30,37</sup>

## Acetazolamide

Carbonic anhydrase inhibitors for urine alkalization have been used when bicarbonate therapy results in metabolic alkalosis with persistent acidic urine.<sup>38</sup> Acetazolamide has theoretical advantages, as it induces bicarbonate diuresis with restorative effects on acid-base status from natriuresis. Case reports show potential benefit, but this has not been confirmed experimentally or clinically and cannot be recommended at this time.<sup>38,39</sup>

## Renal Replacement Therapy

As with causes of renal failure unrelated to rhabdomyolysis, the indications for emergent dialysis or filtration include uncorrectable metabolic acidosis, life-threatening hyperkalemia and other electrolyte disturbances despite medical management, mani-

### Table 2. Steps In The Evaluation And Management Of Rhabdomyolysis

#### Evaluation

- Assess volume status: surrogates to be used include but are not limited to central venous pressure, urine output, dynamic IVC, pulse pressure variation, etc.
- Measure serum CK levels
- Measure serum creatinine and BUN
- Perform urine dipstick with urine sediment analysis
- Investigate causes of rhabdomyolysis

#### Management

- Target urine output of approximately 3 mL/kg/hr
- Check serum K<sup>+</sup> frequently
- Monitor cardiac conduction with ECG, paying attention to changes associated with hyperkalemia
- Correct hypocalcemia only if symptomatic or severe hyperkalemia is present
- Check urine pH; if < 6.5, consider adding bicarbonate to crystalloid infusion
- If resuscitating with saline only, frequently check urine and serum pH and serum chloride levels
- If resuscitating with bicarbonate, frequently check urine and serum pH, serum potassium, sodium, and calcium levels
- Consider mannitol or renal replacement therapy
- Continue volume resuscitation until CK < 1000 U/L and/or myoglobinuria has cleared

Abbreviations: BUN, blood urea nitrogen; CK, creatine phosphokinase, ECG, electrocardiogram; IVC, inferior vena cava; K<sup>+</sup>, potassium; U, units.

festations of uremia, and anuria or oliguria despite aggressive volume expansion with complications related to fluid overload. Fluid overload is particularly problematic when resulting in pulmonary edema or in patients with poor cardiac reserve. Conventional hemodialysis does not filter myoglobin effectively due to its large size, and any potential protective benefit is likely a result of pH changes.

## Controversies And Cutting Edge

Rhabdomyolysis was initially described from autopsies of patients who suffered crush injury, particularly World War II victims.<sup>12</sup> Since that time, rhabdomyolysis has been increasingly linked to a number of conditions unrelated to trauma. Some of these are cited extensively and include alcohol intoxication, illicit drug ingestion, prolonged immobilization and coma, as well as sepsis syndromes. More recently, a number of prescription medications have been implicated. In fact, nearly every class of medication has been described to cause rhabdomyolysis, and much of the most recent literature tends to describe an association between rhabdomyolysis and some therapeutic medications.

HMG-CoA reductase inhibitors (statins) are extensively reported to cause muscle injury and rhabdomyolysis. The precise mechanism is not known, but it is hypothesized to be due to: (1) membrane instability from inhibition of cholesterol synthesis via HMG-CoA reductase inhibition, (2) impaired intracellular protein messaging from abnormally prenylated proteins, and (3) abnormal mitochondrial respiration from coenzyme Q10 deficiency.<sup>40</sup> Many other instances of medication-induced rhabdomyolysis, when known, are either from direct myocyte injury (as is thought to be the case with statins) or indirectly, as in neuroleptic drug-induced neuroleptic malignant syndrome, seizures, or laxative-related electrolyte disturbances.

The evidence for therapeutic measures in rhabdomyolysis is limited. Intravascular volume expansion with crystalloids, with or without urine alkalization, has been the hallmark of treatment for several decades. While outcome data on specific agents such as acetazolamide, furosemide, mannitol, and even urine alkalization are still lacking, immediate and rapid volume expansion remain the evidence-based, first-line therapeutic regimen to mitigate adverse complications of rhabdomyolysis. Newer therapeutic strategies are being tailored to the more recently discovered effect of redox reactions of myoglobin in the proximal tubular cells of the kidney. Antioxidants such as glutathione and vitamin E analogues have shown promise in experimental animal models of myoglobin-induced oxidant injury and may have a future role in management.<sup>41</sup> Aside from antioxidants, there is active research into ways to more rapidly

remove myoglobin from circulation. In case reports, continuous veno-venous hemofiltration or hemodiafiltration has shown promise in removing myoglobin, though prospective randomized trials and outcome data are lacking.<sup>42,43</sup> A recently completed randomized double-blinded trial by Kutsogiannis et al looked at the ability of N-acetylcysteine, as well as continuous renal-replacement therapy, to prevent myoglobinuric renal failure in rhabdomyolysis. The results of this trial have not yet been published ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) identifier: NCT00391911).

## Disposition

The need for aggressive fluid resuscitation and close monitoring of renal function and electrolytes mandates hospital admission in almost all cases. The type of hospital bed is contingent on the etiology of rhabdomyolysis, presence of comorbidities, and severity of illness at presentation. The spectrum of illness is, indeed, very broad.

When severe enough to cause persistent hyperkalemia or fluid overload from aggressive hydration with concomitant severe renal injury and anuria, rhabdomyolysis requires cardiac monitoring and bedside hemodialysis. Patients with compartment syndrome may need immediate fasciotomy and surgical intensive care management. Nonetheless, most cases of rhabdomyolysis are benign and can be managed in unmonitored units.

## Summary

When recognized and treated early, rhabdomyolysis carries an excellent prognosis. With the exception of hyperkalemia-related death or the rare complication of disseminated intravascular coagulation, acute kidney injury is the most serious complication of rhabdomyolysis, regardless of etiology. Mortality data for patients with renal failure vary widely in the literature according to the study population, etiology, presence of multiple

## Risk Management Pitfalls For Rhabdomyolysis (Continued on page 13)

1. **“The urine dipstick is negative for blood, so he cannot have rhabdomyolysis.”**

Urine myoglobin levels are contingent upon the degree of muscle injury, urinary flow rate, volume status of the patient, and time from insult, making the presence of urine myoglobin an insensitive marker of disease presence. Myoglobin is likely to be present early in the course of disease, but it becomes less sensitive the later it is checked.

2. **“The serum is negative for myoglobin; therefore, I’m not concerned about rhabdomyolysis.”**

Myoglobin is released from damaged muscle rapidly and is completely removed from the serum within 24 hours. It has a half-life of only 1 to 3 hours, making serum myoglobin levels unreliable, particularly if not checked in the immediate postinjury phase.

3. **“The patient never complained of muscle pain.”**

The largest case series, to date, have reported that up to half of patients with serologically confirmed rhabdomyolysis lack symptoms referable to the musculoskeletal system. This highlights the importance of awareness of the multitude of causes of rhabdomyolysis, particularly in high-risk circumstances such as drug and alcohol intoxication or prolonged immobility.

4. **“There was no muscle group tenderness or swelling on physical examination.”**

Similar to subjective complaints of muscle pain, objective findings are often lacking. With the exception of cases of crush injury, diagnosis by physical examination alone can be misleading. The volume-depleted status of patients who go on to develop rhabdomyolysis tends to mask the degree of swelling to be expected in cases of severe muscle injury, and it may appear later in the hospital course.

5. **“The serum calcium was low, so I repleted it.”**

The fate of calcium in the pathophysiology of rhabdomyolysis is as follows: initial muscle injury leads to phosphate ion leakage from damaged muscle cells, which precipitates in combination with serum calcium. The calcium phosphate crystals tend to deposit in necrotic muscle, leading to hypocalcemia in the early phase. This early hypocalcemia is followed by late hypercalcemia as the calcium deposited in dead muscle tissue gets remobilized into circulation. The hypocalcemic phase should only be addressed if potassium levels are dangerously high or if severe symptoms of hypocalcemia are present (ie, tetany, cardiac dysrhythmias). Early calcium repletion can exacerbate ectopic calcification in damaged muscle.

causing agents, and comorbidities; however, long-term survival among patients with rhabdomyolysis and acute renal injury tends to be very good when timely management is provided.

## Case Conclusions

The construction worker clearly had developed compartment syndrome of his left lower leg from a crush injury. You appropriately checked compartment pressures, which you noted to be elevated, and informed your orthopedic consultants of the need for immediate fasciotomy. Upon notification of the abnormally elevated CK level, you began aggressive intravascular volume expansion with 0.9% normal saline to reduce the risk of myoglobinuric renal failure. You then checked his serum potassium level, which was 6.4 mEq/L. An ECG was obtained, which did not show any stigmata of hyperkalemia, but you decided to treat with insulin, dextrose infusion, and albuterol 10 mg inhalation by nebulizer because you know dangerous cardiac dysrhythmias can develop when hyperkalemia is

present, even without characteristic ECG findings. The urine pH was 7.2, so you continued aggressive normal saline hydration until the OR suite was ready.

The second patient had clearly developed pneumonia, which was unsuccessfully treated from the previous hospitalization, and now presented with severe sepsis. You treated her with broad-spectrum antibiotics, taking into account her risk for gram-negative bacteria, and started crystalloid infusion to support her hemodynamically. You found that she had developed rhabdomyolysis from sepsis and had already developed acute renal failure, with a BUN:Cr ratio concerning for myoglobinuria-induced renal failure. You checked the urine pH, which was 4.6, and switched her normal saline to 0.45% saline with 2 ampules sodium bicarbonate per liter to alkalinize the urine to a pH > 6.5. You continued early goal-directed therapy, performed endotracheal intubation to decrease her work of breathing, and consulted your intensive care unit for admission.

While it was not surprising that the construction worker had developed rhabdomyolysis, the septic patient may have been more unexpected. You were dealing with

## Risk Management Pitfalls For Rhabdomyolysis (Continued from page 12)

6. **“The ECG was normal, so I didn’t manage the patient’s elevated serum potassium.”**  
The ECG is insensitive in detecting serum potassium elevation. While characteristic ECG findings in hyperkalemia are well documented, several reports of ventricular dysrhythmias from hyperkalemia without preceding ECG stigmata do exist.
7. **“I thought he was just drunk. He looked a little dehydrated, but there’s no way he could have developed rhabdomyolysis from alcohol.”**  
Ethanol can cause rhabdomyolysis by a combination of mechanisms, including immobilization with muscle tissue hypoperfusion and hypoxia, psychomotor agitation (acute ingestion), direct myotoxicity, and electrolyte abnormalities, particularly hypokalemia and hypophosphatemia, which are more common in chronic abuse.
8. **“The patient said his urine was dark, but he said he hasn’t been drinking much water. I thought it was just concentrated from dehydration.”**  
Dark urine is most often a result of dehydration. Occasionally, dark urine may result from conditions with significant morbidity. In addition to rhabdomyolysis, these include, but are not limited to, liver failure with bile pigmenturia, hemoglobinuria from hemolysis,

and hematuria from a variety of nephrogenic causes. A simple urine dipstick or urinalysis with sediment evaluation can efficiently and economically evaluate for these conditions.

9. **“EMS said he had rolled off his bed. I noticed a couple of minor bruises and maybe some skin pressure sores. He was only on the ground for a couple of hours, so he couldn’t possibly have developed rhabdomyolysis.”**  
Prolonged external compression is a well-documented cause of muscle tissue hypoxia. Myocytic hypoxia leads to muscle damage in as little as 2 hours, with irreversible anatomical and functional changes within 4 hours, and necrosis in as little as 6 hours.
10. **“He hasn’t changed any of his medications, so I didn’t think he could have developed rhabdomyolysis.”**  
Nearly every class of medications has been implicated in rhabdomyolysis. The literature on this topic exists mostly in case reports. The exact mechanism is often not known.

rhabdomyolysis in both cases, but some primary disease processes make rhabdomyolysis less of a consideration. Patients often do not present with classic symptoms such as myalgias or extremity swelling, but still carry the same risk of complications from rhabdomyolysis as those who do. The higher the CK level, the greater the damage to muscle, so the septic patient had more muscle injury than the construction worker, despite a more occult cause. While the literature on fluid selection and urine alkalization is still unclear, ample experimental evidence makes bicarbonate therapy a reasonable option, particularly when urine pH is < 6.5. In the first case, you appropriately addressed the other major risk to life, namely hyperkalemia, while in both cases, you gave the patient the best opportunity to recover full renal function.

## References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (\*) next to the number of the reference.

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## CME Questions



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1. **During extremes of physical activity, skeletal muscle can consume what percentage of the total body requirement of oxygen to produce enough ATP?**
  - a. 10%
  - b. 20%
  - c. 85%
  - d. 100%
2. **According to most of the largest case series, which etiological factor is the most commonly associated with rhabdomyolysis?**
  - a. Head injury
  - b. Insect bite
  - c. Viral infection
  - d. Drug and/or alcohol intoxication
3. **Patients report experiencing myalgias in more than 80% of confirmed cases of rhabdomyolysis.**
  - a. True
  - b. False
4. **How is rhabdomyolysis conclusively diagnosed?**
  - a. Serologic testing
  - b. Patient-reported symptoms
  - c. First responder reports
  - d. ECG
5. **In rhabdomyolysis, serum myoglobin levels peak in:**
  - a. 1 to 3 hours
  - b. 8 to 12 hours
  - c. 12 to 24 hours
  - d. 24 to 48 hours
6. **Early complications of rhabdomyolysis include:**
  - a. Acute kidney injury
  - b. Disseminated intravascular coagulation
  - c. Death
  - d. Compartment syndrome
7. **If a crush injury victim is likely to face a prolonged extrication time, fluid resuscitation should be initiated before complete extrication.**
  - a. True
  - b. False
8. **The evidence-based, first-line treatment to mitigate adverse effects of rhabdomyolysis is:**
  - a. Furosemide
  - b. Mannitol
  - c. Urine alkalization
  - d. Rapid volume expansion

# Emergency Medicine Practice has been accepted for indexing on PubMed

We are proud to announce that our inaugural publication, *Emergency Medicine Practice*, has been accepted by the National Library of Medicine for MEDLINE® indexing. This means that all 2011 and future issues of *Emergency Medicine Practice* will be indexed on PubMed. This is an important breakthrough for our publication, and we are extremely pleased to have received this recognition.

To read a letter from Dr. Andy Jagoda, Editor-in-Chief, about this exciting achievement, please visit [www.ebmedicine.net/MEDLINEletter](http://www.ebmedicine.net/MEDLINEletter).

All of our readers have played an instrumental role in ensuring the publication's high quality, and we greatly appreciate your support.

—THE EB MEDICINE TEAM



## Physician CME Information

**Date of Original Release:** March 1, 2012. Date of most recent review: February 10, 2012. Termination date: March 1, 2015.

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**Target Audience:** This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

**Goals:** Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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