Rhabdomyolysis: Perioperative Considerations

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LESSON OBJECTIVES
Upon completion of this lesson, the reader should be able to:

1. Explain the concept of rhabdomyolysis.
2. Describe the pathophysiology of the condition.
3. Identify the multiple causes of rhabdomyolysis.
4. List the special features of intraoperative rhabdomyolysis.
5. Discuss the role of serum creatine kinase measurement and assessment for myoglobinuria in the diagnosis of rhabdomyolysis.
6. Describe the clinical manifestations of rhabdomyolysis.
7. Enumerate the life-threatening sequelae of rhabdomyolysis including acute kidney injury and metabolic derangements.
8. Discuss the treatment approaches to rhabdomyolysis.
9. Analyze the suboptimal evidence for some of the common interventions.
10. Describe the treatment of intraoperative rhabdomyolysis.

Current Reviews in Clinical Anesthesia® designates this lesson for 1½ CME credit hours in pharmacology/therapeutics.

Introduction
Rhabdomyolysis is the dissolution of striated (skeletal) muscle. It is characterized by the leakage of muscle cell components (including electrolytes, myoglobin, creatine kinase, lactate dehydrogenase, aldolase, alanine aminotransferase, and aspartate aminotransferase) into the circulation. It may occur as a result of traumatic or non-traumatic events, and may develop intraoperatively. Independent of the etiology, massive muscle necrosis can occur, manifesting as myalgia, swelling, limb weakness and pigment in the urine. Rhabdomyolysis may cause acute renal failure and life-threatening hyperkalemia and hypocalcemia.

There are multiple scenarios under which anesthesiologists may encounter rhabdomyolysis, ranging from the trauma victim with crush injury to the patient with status epilepticus after neurosurgery, from the “vasculopath” with an ischemic leg and compartment syndrome to an individual who develops malignant hyperthermia. This lesson will discuss the pathogenesis and etiology of rhabdomyolysis, detail the associated complications and treatments, and provide guidance on perioperative management.

Pathophysiology
Low levels of calcium are present in the sarcoplasm (muscle cell cytoplasm) at rest and increase quickly to allow actin-myosin binding and muscle contraction when required. The calcium concentration in muscle cells is tightly controlled by a series of pumps, channels and exchangers. Adenosine triphosphate
(ATP) is required to maintain the integrity of these control mechanisms, and for muscle function. Aerobic ATP generation accounts for 30% of the body's oxygen consumption at rest and up to 85% at extremes of physical activity. Anaerobic ATP generation—in which glycogen is transformed to lactate in the absence of oxygen—occurs in skeletal muscles under certain conditions (e.g., physiologically during extremes of exercise or pathologically during limb ischemia). **Rhabdomyolysis results from a disruption of the membrane (the sarcolemma) of skeletal muscle cells, leading to an unregulated influx of calcium.** The sarcolemma can be disrupted directly (e.g., by trauma) or as a result of an ATP supply-demand mismatch (inadequate generation or excessive consumption). The persistent increase in intracellular calcium leads to sustained contraction and the activation of calcium-dependent proteases and phospholipases, with subsequent destruction of cell components and cellular destruction (Figure 1). In the case of trauma, additional ischemia-reperfusion and neutrophil-induced inflammatory injuries occur.

**Creatine Kinase (CK) and Myoglobin**

In the intact cell—especially skeletal muscle cells—creatine kinase (CK)—also known as creatine phosphokinase (CPK)—is the enzyme responsible for the reversible reaction:

\[
\text{Creatine + ATP} \rightarrow \text{Phosphocreatine + ADP}
\]

This reaction allows for the storage and generation of ATP and thus facilitates a cellular “energy reservoir”. **Destruction of myocytes causes leakage of enzymes and cellular components (including CK and myoglobin) into the circulation.** An elevated serum concentration of CK is the hallmark of rhabdomyolysis. CK has a serum half-life of 1.5 days. It is elevated in the first 12 hours after muscle injury, peaks during the first 3 days, and normalizes after about 5 days (Figure 2). The degree of CK elevation correlates with the degree of muscle injury.

Myoglobin is a dark-red protein with molecular weight 17.5 kDa that is primarily responsible for transportation of oxygen to skeletal muscles. It is composed of globin and one molecule of heme and can carry one oxygen molecule (in contrast to hemoglobin which can carry 4 oxygen molecules). Myoglobin was the first protein to have its structure elucidated by X-ray crystallography—in 1958. During rhabdomyolysis, myoglobin is released into the blood and can be used as a marker of muscle injury, but its serum half-life is only 1-3 hours and it is completely absent by 24 hours, so it is unreliable for diagnosis. Myoglobin is filtered by the kidney and when the serum myoglobin concentration increases, the renal filtration capacity is quickly overwhelmed and myo-
globin appears in the urine (where it may be detected on urine dipstick as positive for blood). Myoglobinuria occurs only in rhabdomyolysis, and myoglobin is nephrotoxic (see below).

**Rhabdomyolysis, the dissolution of skeletal muscle, is characterized by leakage of cell components into the circulation.**

**Etiology**

The causes of rhabdomyolysis can be divided into three broad categories: traumatic or muscle compression (e.g., crush injury, prolonged immobilization); non-traumatic exertional (e.g., marked exertion in untrained individuals, hyperthermia, metabolic myopathies); non-traumatic non-exertional (e.g., infections, drugs and toxins, electrolyte disorders). Another system of categorization with causes is provided in Table 1. The cause is often readily identifiable. When it is not obvious, the precipitant can often be ascertained through a careful history, physical examination, and laboratory analyses. The relative frequencies of the different etiologies of rhabdomyolysis differ depending on the study population. In a study of 2,371 patients (reported by McMahon), the most frequently associated conditions were trauma (26%), immobilization (18%), sepsis (10%), vascular surgery (8%) and cardiac surgery (6%). However, in the series of 475 patients (reported by Melli), the most common cause was exogenous toxins (46%), including alcohol and illicit drugs (34%) and medications (15%). Myopathies and metabolic defects were seen in 10% of cases. Many patients have more than one etiologic factor.

**Anesthesia-related Rhabdomyolysis**

Rhabdomyolysis is a component of the clinical manifestations of malignant hyperthermia (MH), the clinical presentation and treatment of which is familiar to anesthesia providers. As reviewed by Capacchione and Muldoon, there is likely some overlap between exertional heat illness, exertional rhabdomyolysis, and MH.

There are other causes of anesthesia-induced rhabdomyolysis. Patients with dystrophinopathies (Duchenne and Becker muscular dystrophies) can develop rhabdomyolysis and MH-like signs after exposure to MH triggering agents (e.g., succinylcholine). They do not develop MH itself—they do not have ryanodine receptor abnormalities. In such patients the absence of the dystrophin-glycoprotein complex results in sarcolemmal instability, giving rise to increased intracellular calcium concentration and massive potassium release. Anesthetic-induced rhabdomyolysis can occur without the hypermetabolism and may present suddenly as hyperkalemia-induced cardiac arrest. Unlike in MH when dantrolene is clearly indicated, in non-MH anesthesia-
induced rhabdomyolysis, dantrolene is unlikely to have any effect as it is not a membrane stabilizer. Prophylactic use of a total intravenous anesthetic is recommended in patients with dystrophinopathies, although the level of evidence is weak, being based on case reports and expert opinion.

Table 1: Causes of Rhabdomyolysis
(Data from Bosch, Poch & Grau, 2009 and Parekh, 2010)

<table>
<thead>
<tr>
<th>Category</th>
<th>Common Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trauma</strong></td>
<td>Crush injury</td>
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<td></td>
<td>Burn injury</td>
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<td><strong>Exertion, excessive muscle activity</strong></td>
<td>Seizures</td>
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<td></td>
<td>Strenuous exercise</td>
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<td></td>
<td>Alcohol withdrawal</td>
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<td></td>
<td>Status asthmaticus (especially in children)</td>
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<td><strong>Muscle hypoxia</strong></td>
<td>Major artery occlusion</td>
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<td></td>
<td>Limb compression</td>
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<tr>
<td><strong>Body temperature changes</strong></td>
<td>Malignant hyperthermia</td>
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<tr>
<td></td>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td></td>
<td>Exertional heat illness (with hyperthermia)</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
</tr>
<tr>
<td></td>
<td>Electrical injury (a combination of thermal injury and direct injury)</td>
</tr>
<tr>
<td><strong>Genetic defects</strong></td>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td></td>
<td>Disorders of glycolysis or glycogenolysis</td>
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<tr>
<td></td>
<td>Disorders of lipid metabolism</td>
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<td></td>
<td>Mitochondrial disorders</td>
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<td></td>
<td>Pentose phosphate pathway disorders</td>
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<tr>
<td></td>
<td>Purine nucleotide cycle disorders</td>
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<tr>
<td><strong>Infections</strong></td>
<td>Influenza A and B</td>
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<tr>
<td></td>
<td>Epstein-Barr virus</td>
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<td>Coxsackie virus</td>
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<td></td>
<td>Primary HIV infection</td>
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<td></td>
<td>Legionella</td>
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<tr>
<td></td>
<td>Strep pyogenes</td>
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<tr>
<td></td>
<td>Staph aureus pyomyositis</td>
</tr>
<tr>
<td></td>
<td>Clostridium</td>
</tr>
<tr>
<td></td>
<td>Viral myositis</td>
</tr>
<tr>
<td><strong>Metabolic and electrolyte disorders</strong></td>
<td>Hypokalemia (low potassium levels can lead to localized microvascular vasoconstriction)</td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia (because of phosphate requirement to generate ATP)</td>
</tr>
<tr>
<td></td>
<td>Hypernatremia (in endurance athletes and psychogenic polydipsia)</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>Non-ketotic hyperosmolar state</td>
</tr>
<tr>
<td></td>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td><strong>Drugs and toxins</strong> (direct effects and immobilization effects)</td>
<td>Statins (hypothesized to be secondary to membrane instability because of inhibition of cholesterol synthesis)</td>
</tr>
<tr>
<td></td>
<td>Fibrates</td>
</tr>
<tr>
<td></td>
<td>Succinylcholine</td>
</tr>
<tr>
<td></td>
<td>Volatile anesthetics</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
</tr>
<tr>
<td></td>
<td>Heroin</td>
</tr>
<tr>
<td></td>
<td>Amphetamines</td>
</tr>
<tr>
<td></td>
<td>Methylenedioxymethamphetamine (MDMA) (&quot;ecstasy&quot;)</td>
</tr>
<tr>
<td></td>
<td>LSD</td>
</tr>
<tr>
<td></td>
<td>Anti-psychotics</td>
</tr>
<tr>
<td></td>
<td>Snakebites</td>
</tr>
<tr>
<td></td>
<td>Africanized bees</td>
</tr>
<tr>
<td><strong>Connective tissue diseases</strong></td>
<td>Polymyositis</td>
</tr>
<tr>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td>Sjogren’s syndrome</td>
</tr>
<tr>
<td><strong>Idiopathic</strong></td>
<td>May be recurrent</td>
</tr>
</tbody>
</table>
Although not related directly to anesthetic drugs, rhabdomyolysis may also develop perioperatively because of intraoperative positioning and immobility. There are multiple reports of the development of rhabdomyolysis—of varying degrees of severity—during general anesthesia, especially in morbidly obese patients undergoing laparoscopic or robotic surgery. Prolonged position-dependent muscle compression during lengthy procedures is believed to be the cause. The use of general anesthesia and muscle relaxants prevents patients from shifting their weight to relieve the pressure on dependent areas. In non-obese patients, exaggerated lithotomy, knee-chest and lateral decubitus positioning may result in rhabdomyolysis. Even patients in the supine position may not be immune if the procedure is markedly prolonged.

Clinical Manifestations
Myalgias, muscle weakness and the presence of red-brown urine (myoglobinuria) constitute the “characteristic triad” of rhabdomyolysis. There is a wide spectrum of severity, however, and a variety of presentations. More than half of patients do not report muscle symptoms. The clinical manifestations of rhabdomyolysis are presented in Table 2. Rhabdomyolysis-induced acute kidney injury (AKI), compartment syndrome, and electrolyte imbalances deserve special note.

Myalgias, muscle weakness, and the presence of red-brown urine (myoglobinuria) constitute the “characteristic triad” of rhabdomyolysis.

Acute Kidney Injury (AKI)
Both traumatic and non-traumatic rhabdomyolysis may cause acute kidney injury (AKI) and the associated electrolyte disturbances may be life-threatening. The complication is relatively common, occurring in 46% of 475 patients with rhabdomyolysis reported by Melli (and was especially common in those with rhabdomyolysis after trauma or illicit drug use). Rhabdomyolysis-induced AKI represents about 7-10% of all cases of AKI in the U.S. Myoglobin concentrates along the renal tubules, but does not have a marked nephrotoxic effect unless the urine is acidic. In acidic conditions, however, myoglobin precipitates when it interacts with the Tamm-Horsfall tubular protein, leading to direct tubule cytotoxicity proximally, and tubular obstruction by casts distally. Renal vasoconstriction also plays a role in the development of rhabdomyolysis-induced renal injury. Table 3 provides suggestions for the prevention and treatment of AKI in rhabdomyolysis.

Compartment Syndrome
The limb muscle groups are divided into sections (compartments) formed by strong fascial membranes. Rhabdomyolysis-associated influx of fluid into skeletal muscle causes swelling that may lead to increases in intracompartmental pressure. This causes muscle ischemia, resulting in more rhabdomyolysis, which in turn worsens the swelling and sets up a vicious cycle. A tense painful muscle compartment should suggest compartment syndrome. Associated features include pain out of proportion to the apparent injury or pain with passive movement, paresthesias, decreased sensation, and motor weakness. Although not required for diagnosis, measurement of compartment pressures can confirm the diagnosis. A “delta pressure” (diastolic blood pressure–compartment pressure) of 30 mmHg or less indicates the presence of compartment syndrome. Emergent fasciotomy is required.

Rhabdomyolysis may be caused by certain anesthetics and may develop perioperatively because of intraoperative positioning and immobility.

Electrolyte Abnormalities
Hyperkalemia and hyperphosphatemia occur because of the rapid release of potassium and phosphate from damaged muscle cells. Hyperkalemia may quickly become life-threatening, especially if rhabdomyolysis-induced renal failure develops. In the absence of oliguric AKI, potassium and phosphate levels decrease as they are excreted in the urine. Hypocalcemia occurs early in rhabdomyolysis because of calcium influx into damaged myocytes, deposition of calcium salts in damaged muscle, and decreased bone responsiveness to parathyroid hormone. Severe hypocalcemia may precipitate hypocalcemic tetany, seizures, or cardiac arrhythmias. After the first few days, calcium levels may increase as the muscles give up sequestered calcium. Hyperuricemia can occur because of purine release from damaged myocytes and decreased urinary excretion in renal dysfunction. A metabolic acidosis with increased anion gap typically occurs.

Diagnosis
The diagnosis of rhabdomyolysis may be made in a patient with either an acute neuromuscular illness or dark urine without other symptoms, plus a marked elevation in serum CK (at least 5 times normal, but typically in the tens of thousands range). Anesthesiologists will usually see patients with acute rhabdomyolysis when the diagnosis is typically already made or suspected because of the clinical context. If the CK elevation is acute and myoglobinuria is present, the diagnosis can be made with confidence. (Although other muscle enzymes such as aldolase, aminotransferases and lactate dehydrogenase are typically elevated, such testing is
More subtle presentations and recurrent episodes may be indicative of a metabolic myopathy. Myoglobinuria may be identified on routine urine dipstick examination combined with microscopic examination. Unspun urine or the supernatant of centrifuged urine will be positive for “heme” on dipstick if myoglobinuria is present. Microscopic examination of the urine sediment should exclude the presence of red blood cells as a cause for heme-positive urine.

**Table 2: Clinical Manifestations of Rhabdomyolysis**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Laboratory abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Myalgias</em></td>
<td>Red-brown urine*</td>
<td>Elevated serum CK (usually at least 5 times normal on presentation; may be in the tens of 1000s range; typically almost entirely the MM fraction)</td>
</tr>
<tr>
<td>May be severe, may be absent</td>
<td>Fever</td>
<td>Elevations of other muscle enzymes including aminotransferases and aldolase</td>
</tr>
<tr>
<td>Especially in proximal muscle groups, lower back and calves</td>
<td>Tachycardia</td>
<td>Myoglobinuria (positive for “blood” on urinary dipstick, but urine microscopy shows only a few red blood cells)</td>
</tr>
<tr>
<td>Muscle stiffness, cramping</td>
<td>Vomiting</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Malaise</td>
<td>Muscle weakness*</td>
<td>Hypoventilation (extracellular fluid influx into injured muscles leads to intravascular volume depletion, increasing the chance of AKI)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Muscle tenderness</td>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>Nausea</td>
<td>Muscle swelling (especially with fluid repletion)</td>
<td>• Hyperkalemia and hyperphosphatemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Both are released from muscle cells. Rapidly developing hyperkalemia may be life-threatening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypocalcemia and hypercalcemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• During the first few days after the development of rhabdomyolysis calcium enters damaged myocytes, potentially leading to extreme hypocalcemia. Deposition of calcium salts also occurs (ectopic calcification). During recovery, serum calcium levels rebound and may overshoot.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperuricemia (due to release of purines from damaged muscle cells and reduced urinary excretion in the presence of AKI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Infrequent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Occurs due to release of tissue thromboplastin and other prothrombotic substances from injured muscle cells</td>
</tr>
</tbody>
</table>

*Myalgias, muscle weakness and the presence of red-brown urine (myoglobinuria) constitute the “characteristic triad” of rhabdomyolysis.*
Management

Treatment of a Reversible Cause
If there is a reversible cause or if muscle injury is ongoing, steps must be taken urgently to deal with the cause. For example, in a patient with an ischemic limb, revascularization should be attempted as a matter of priority. Thus, patients may present emergently to the operating room or the interventional radiology suite for procedures requiring sedation or general anesthesia. Patients with compartment syndrome should undergo urgent fasciotomy. Therapy for exertional heat illness includes cooling and supportive measures. In many cases, however, there are limited opportunities to intervene and/or muscle damage may have occurred by the time of presentation.

Fluid Resuscitation
The mainstay of therapy for patients with rhabdomyolysis is volume resuscitation to replenish intravascular volume lost due to sequestration of fluid in the injured muscles. Aggressive volume resuscitation, coupled with optimization of hemodynamics and achieving a brisk urine output, may prevent the development of AKI. In traumatic injuries—especially crush injuries—fluid resuscitation prior to extrication of a trapped, injured limb will mitigate fluid loss to the injured limb when perfusion is restored. A delay in fluid resuscitation has been reported in case control studies of earthquake victims with crush injuries to increase the incidence of renal failure. In a normal-sized adult, 10 L of fluid may be required to restore intravascular volume. Urine output should ideally be at least 3 ml/kg/hr to flush myoglobin from the renal tubules and avoid precipitation and tubular obstruction. The specific fluid used for resuscitation remains a matter of debate. Isotonic crystalloid solutions (e.g., 0.9% NaCl, lactated Ringer’s) are usually favored. Large volumes of normal saline cause a hyperchloremic metabolic acidosis and lactated Ringer’s contains (a small amount of) potassium, so neither is a perfect choice in these circumstances. Sodium bicarbonate-containing solutions have also been used to alkalize the urine (see below).

Alkalinization of the Urine
As previously mentioned, myoglobin precipitates in renal tubules under acidic conditions. Furthermore, there is some experimental evidence that the mechanisms of renal toxicity are more potent in an acid milieu. Thus, the administration of sodium bicarbonate solutions as part of the resuscitation fluid has been advocated to cause “alkalinization” of the urine to a pH greater than 6.5 in concert with a serum pH of 7.4-7.45. Despite a theoretical rationale for alkalization, the clinical benefits have not been demonstrated in a study robust enough to satisfy most experts, either because sodium bicarbonate was used in association with other measures (e.g., diuretics) or the results were not convincing. For example, in a study of 2,083 victims of trauma by Brown et al, rhabdomyolysis developed in 85%, and the administration of sodium bicarbonate (plus mannitol) did not prevent renal failure, the need for dialysis, or death. (There was a suggestion, however, that there may have been a beneficial effect in patients with CK values > 30,000 U/L.) Although the alkalemia it causes may worsen pre-existing hypocalcemia, sodium bicarbonate therapy is relatively benign and administration of a combination of normal saline and sodium bicarbonate (e.g., 100 mEq NaHCO₃ in 1 L 0.45% NaCl) is a reasonable approach to replenishing fluid in patients with rhab-

Table 3: Suggestions for the Prevention and Treatment of Rhabdomyolysis-induced Acute Kidney Injury.
(Data from Bosch, Poch & Grau, 2009)

- Assess volume status
- Measure serum CK
- Measure plasma and urine creatinine, potassium, sodium, total and ionized calcium, BUN, magnesium, phosphate, urine acid, albumin, arterial blood gas, complete blood count, coagulation studies
- Perform urine dipstick test and urine sediment microscopy
- Promptly initiate volume repletion with normal saline (infuse at 200–1000 ml/hr, depending on clinical context and patient condition; 400 ml/hr in an adult is a reasonable starting rate)
- Target urine output of 3 ml/kg/hr
- Check serial potassium levels
- Correct hypocalcemia only if symptomatic (seizures, tetany) or if severe hyperkalemia
- Investigate the cause of rhabdomyolysis
  - If urine pH is less than 6.5, alternate each liter of normal saline with 1 L 5% dextrose with 100 mEq NaHCO₃
  - Consider treatment with mannitol (up to 200 g/day). Monitor by checking plasma osmolality
  - Maintain volume repletion until myoglobinuria has cleared
  - Consider renal replacement therapy for resistant or rapidly worsening hyperkalemia, oliguria or anuria, volume overload, or resistant metabolic acidosis

domyolysis, especially when metabolic acidosis is present.

**Correction of Electrolyte Imbalance**

Rhabdomyolysis-induced hyperkalemia may be life-threatening because of its severity and rapidity of development. Successful management of hyperkalemia is one of the key elements of management of rhabdomyolysis. Table 4 provides an approach to management. Hypocalcemia can also be dangerous and replacement is required for critically low concentrations. It should be borne in mind, however, that the hypocalcemia in the early days after the development of rhabdomyolysis will give way to normal or even high concentrations later as sequestered calcium is released from muscles.

**Diuresis**

Although a brisk urine output is desirable, diuretics should not be used until fluid repletion has been achieved. The osmotic diuretic mannitol increases urinary flow (thus flushing nephrotoxins through the renal tubules), extracts fluid that has accumulated in injured muscles, and is a free-radical scavenger. Animal studies have suggested a renal protective effect related to its diuretic action, but this has not been confirmed by a randomized trial in humans. Nonetheless, many experts advocate the administration of mannitol in patients with rhabdomyolysis, while monitoring plasma osmolality and the osmolar gap to ensure safety. Loop diuretics, similarly, have not been demonstrated to have an outcome benefit despite the theoretical support for their use. They may be used in a fashion similar to their use in non-rhabdomyolysis-induced AKI.

**Rhabdomyolysis may cause acute renal failure and life-threatening hyperkalemia and hypocalcemia.**

**Renal Replacement Therapy**

**Indications for hemodialysis in patients with rhabdomyolysis include severe or refractory hyperkalemia, severe or rapidly developing metabolic acidosis, and volume overload with respiratory compromise.** The method of renal replacement therapy is dependent on multiple factors, especially the patient’s hemodynamic status. If the patient is hemodynamically unstable—e.g., a patient with shock after trauma—continuous renal replacement therapy (CRRT) (continuous venovenous hemofiltration or hemodiafiltration) may be used. Although CRRT causes less hemodynamic fluctuations than intermittent hemodialysis (IHD), this method is less efficient at correcting metabolic derangements and removing fluid. Thus, IHD is preferred when the patient has acceptable hemodynamics, especially when hyperkalemia or volume overload needs to be treated urgently. Conventional hemodialysis does not remove myoglobin effectively, and “preventive” hemofiltration (i.e., in the absence of the usual indications for dialysis) lacks supportive evidence.

**Anesthetic Management**

The anesthesiologist may encounter patients with rhabdomyolysis in a variety of situations. In the acute setting, patients who have suffered traumatic crush injuries with associated rhabdomyolysis may present emergently for laparotomy or orthopedic surgery, and individuals with ischemic limbs and rhabdomyolysis may require emergent revascularization and the performance of fasciotomies. On an elective basis, patients who have suffered rhabdomyolysis and the consequences thereof may present to the interventional radiology suite for long-term dialysis catheter placement, or to the operating room for plastic surgical or orthopedic procedures related to muscle injury and wound care. Anesthesia considerations for the acute setting follow.

**The mainstay of therapy for patients with rhabdomyolysis is volume resuscitation to replenish intravascular volume lost due to sequestration of fluid in the injured muscles.**

The nature of the surgical emergency and the condition of the patient will be the major influences on anesthetic technique. This is true for patients with or without rhabdomyolysis. As a general principle for patients with acute rhabdomyolysis, one must consider the possibility of rhabdomyolysis-induced intravascular volume depletion and the potential for anesthesia-induced cardiovascular collapse during induction. Appropriate induction agents should be chosen with this in mind, and one should ensure the availability of vasopressor and inotropic agents, both in bolus and infusion form. Administration of succinylcholine may precipitate life-threatening hyperkalemia in a patient with muscle injury and/or acute kidney injury and is best avoided. Use of a high dose of a non-depolarizing muscle relaxant (e.g., rocuronium) is preferred for rapid sequence techniques. There should be a very low threshold for placement of an arterial catheter in patients with rhabdomyolysis for blood pressure monitoring in the setting of potential hemodynamic instability and for serial evaluation of acid-base status and electrolytes. Central venous access is often useful for infusion of vasoactive agents, administration of calcium and sodium bicarbonate which may be necessary in the treatment of hyperkalemia, and for evaluation of central venous pressure to aid with volume resuscitation. Placement of a large bore dialysis catheter
may be necessary pre-, intra-, or postoperatively. The internal jugular vein is preferred, the right sided being used more commonly. Placement of a short-term dialysis catheter in the subclavian vein is best avoided as such positioning may lead to stenosis and complicate future extremity arterio-venous fistula formation, if and when long-term dialysis access is required.

Intraoperative management of patients with rhabdomyolysis should be in the context of a continuum of care involving the emergency department, operating room, and intensive care unit. Resuscitative and therapeutic measures (e.g., volume administration, treatment of electrolyte imbalances) and interventions to decrease the risk of AKI (e.g., urine alkalization, diuresis after replenishment of intravascular volume) that have been initiated preoperatively should be continued intraoperatively and beyond.

### Table 4: Investigation and Management of Rhabdomyolysis-induced Hyperkalemia
(Modified from Bosch, Poch & Grau, 2009)

- Serial assessment of serum K⁺ concentrations should be performed, at least every 4 hours in patients with severe rhabdomyolysis.
- Rapidly rising K⁺ levels should be treated aggressively.
- The ECG should be evaluated for manifestations of hyperkalemia, which include QRS widening, diminished P waves, “sine-waves”, arrhythmias (e.g., ventricular tachycardia).
- Intensive care unit admission should occur if the K⁺ concentration is greater than 6 mEq/L, is rapidly increasing, if hyperkalemia-related ECG changes are seen, or if rhabdomyolysis is severe (CK levels > 60,000 IU/L).
- Serum calcium concentrations should be measured, as hypocalcemia aggravates the adverse clinical effects of hyperkalemia.
- If the ECG demonstrates hyperkalemia-related abnormalities, calcium chloride or calcium gluconate should be administered intravenously. Multiple doses and/or a continuous infusion may be required. This therapy, of course, may worsen the hypercalcemia that may develop during the later stage of rhabdomyolysis, but in the short-term calcium is essential to mitigate the adverse effects of K⁺ on the myocardium.
- Therapeutic interventions to shift K⁺ from the extracellular fluid into cells should be undertaken if K⁺ is greater than 6 mEq/L and/or is rising quickly. Such measures include administration of:
  - Insulin and dextrose
  - Beta-2-adrenergic agents (e.g., albuterol by nebulizer or metered-dose inhaler through the breathing circuit). Use of beta-2-agonists may, however, worsen cardiac arrhythmias.
  - Sodium bicarbonate (although this treatment may worsen the manifestations of hypocalcemia)
  - Note that beta-2-agonist administration and sodium bicarbonate administration should not be used as isolated interventions.

#### Interventions to remove K⁺ from the body include:
- Administration of a loop diuretic (e.g., furosemide). Such therapy should be employed only after repletion of intravascular volume and may be ineffective if acute kidney injury has developed and the kidneys are unresponsive to diuretics.
- Hemodialysis, which should be initiated if the hyperkalemia is refractory to other measures or is severe. Serum K⁺ should be rechecked 4 hours after dialysis, as rebound hyperkalemia may occur.
- Cation-exchange resins (sodium polystyrene sulfonate) (e.g., Kayexalate, Kionix) may be administered orally or as enemas. Their use may be associated with significant complications, however, and they are used less frequently than in the past.

### Treatment of Anesthetic-related Rhabdomyolysis

Obviously prevention is better than cure, so avoidance of triggering agents in patients with a genetic predisposition to MH or non-MH-related rhabdomyolysis (e.g., Duchenne muscular dystrophy) is key. Rhabdomyolysis in the setting of MH should be treated with dantrolene and supportive measures in the usual fashion, a full discussion of which is beyond the scope of this lesson. In the case of anesthetic-induced rhabdomyolysis that is not associated with MH, treatment will depend on the presentation. Acute hyperkalemic cardiac arrest (as may occur in patients with Duchenne or Becker muscular dystrophy after administration of succinylcholine) should be treated with defibrillation or cardioversion for ventricular fibrillation or ventricular tachycardia, respectively, hyperventilation, and administration of intravenous calcium (multiple doses are likely to be
required), sodium bicarbonate and insulin/dextrose. The development of a hypermetabolic state should be treated with supportive measures including hyperventilation to compensate for carbon dioxide generation, cooling, fluid resuscitation, and correction of acidosis, in a fashion similar to the treatment of MH, with the caveat that—as previously mentioned—dantrolene is not likely to be helpful in such cases.

**Intraoperative management of patients with rhabdomyolysis should be in the context of a continuum of care involving the emergency department, operating room, and intensive care unit.**

**Prognosis**

In the absence of renal failure, the prognosis for patients with rhabdomyolysis is good, although the outcome is somewhat dependent on the etiology of the rhabdomyolysis. For example, rhabdomyolysis in association with vasculopathy-induced limb ischemia carries a much higher incidence of mortality (approximately 30%) than rhabdomyolysis associated with illicit drug use (less than 5%). The development of renal failure in patients with rhabdomyolysis significantly increases mortality, especially in the most seriously ill. In a study of patients with rhabdomyolysis who required ICU care, the mortality with and without AKI was 59% and 22%, respectively. More reassuringly, however, for all patients with rhabdomyolysis and associated AKI, long-term survival is close to 80%, and the majority of patients recover renal function.

**Summary**

Rhabdomyolysis is a potentially life-threatening condition in which destruction of skeletal muscle cells leads to massive influx of fluid. At the same time cellular content, including CK and myoglobin, leaks out of the cells. The condition may result from traumatic and non-traumatic causes. Rhabdomyolysis may be caused by certain anesthetics in patients with a genetic predisposition, or may develop perioperatively because of intraoperative positioning and immobility. Myalgias, muscle weakness, and the presence of red-brown urine (myoglobinuria) constitute the “characteristic triad” of rhabdomyolysis. Plasma CK values may be in the tens of thousands. Acute renal failure and life-threatening hyperkalemia and hypocalcemia may occur. The mainstay of therapy for patients with rhabdomyolysis is volume resuscitation to replenish losses due to sequestration of fluid in the injured muscles. Other potential therapies aimed at preventing renal failure include administration of diuretics and alkalization of the urine. Correction of electrolyte and metabolic imbalances may require renal replacement therapy. Intraoperative management of patients with rhabdomyolysis should be in the context of a continuum of care involving the emergency department, operating room, and intensive care unit. If properly managed, the prognosis is good, although this is somewhat etiology-dependent.

**References**


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Dr. Keegan is Professor of Anesthesiology at Mayo Clinic College of Medicine and Consultant Anesthesiologist and Intensivist at Mayo Clinic, Rochester, MN. He graduated from Trinity College Medical School in Dublin, Ireland in 1992. After completing a residency in Internal Medicine in Ireland and becoming a Member of the Royal College of Physicians of Ireland, Dr. Keegan moved to Mayo Clinic in Rochester. He completed a residency in Anesthesiology and then a fellowship in Critical Care Medicine as a Mayo Special Clinical Scholar. He joined the Mayo Staff as a consultant in 2001. His clinical interests include critical care medicine and liver transplant anesthesia.

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He lives with his wife and children in Rochester, Minnesota.

Tips for your Clinical Practice: Key Points

- The “classical triad” of rhabdomyolysis includes myalgias, muscle weakness, and the presence of brown urine.
- Rhabdomyolysis may cause acute renal failure (AKI) and life-threatening hyperkalemia and hypocalcemia.
- The mainstay of therapy for patients with rhabdomyolysis is volume resuscitation to replenish fluid losses due to sequestration of fluid in the muscles.
- To prevent AKI, administration of diuretics and alkalinization of the urine is recommended.
- Rhabdomyolysis of varying degrees can develop during general anesthesia because of prolonged position-dependent muscle compression, especially in obese patients during prolonged procedures.
- Acute hyperkalemia during anesthesia should initially be treated with intravenous calcium; multiple doses may be required.

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POST-STUDY QUESTIONS

1. Uncontrolled entry of which electrolyte into the sarcoplasm is the major pathophysiologic event in rhabdomyolysis?
   □ A. Sodium.
   □ B. Calcium.
   □ C. Magnesium.
   □ D. Potassium.

2. Depletion of which intracellular compound is the major factor in the development of rhabdomyolysis?
   □ A. Tumor necrosis factor.
   □ B. Lipoprotein A.
   □ C. Adenosine triphosphate.
   □ D. Glucose-6-phosphate.

3. An increase of which serum component is a key step in the diagnosis of rhabdomyolysis?
   □ A. Creatine kinase.
   □ B. Aldolase.
   □ C. Magnesium.
   □ D. Hemoglobin.

4. Administration of which medication to patients with Becker muscular dystrophy may lead to rhabdomyolysis?
   □ A. Rocuronium.
   □ B. Propofol.
   □ C. Succinylcholine.
   □ D. Ketamine.

5. Which constellation of signs and symptoms constitutes the “classical triad” of rhabdomyolysis?
   □ A. Respiratory failure, ventricular tachycardia, abdominal distension.
   □ B. Myalgias, somnolence, hematuria.
   □ C. Myalgias, muscle weakness, red-brown urine.
   □ D. Tetany, muscle weakness, polyuria.

6. Which derangement on blood gas analysis is most characteristic of rhabdomyolysis?
   □ A. Respiratory acidosis.
   □ B. Metabolic alkalosis.
   □ C. Respiratory alkalosis.
   □ D. Metabolic acidosis.

7. Which therapy removes potassium FROM THE BODY?
   □ A. Intravenous dextrose and insulin.
   □ B. Hemodialysis.
   □ C. Nebulized albuterol.
   □ D. Intravenous sodium bicarbonate.

8. Based on studies of patients with crush injuries after earthquakes, which statement is TRUE?
   □ A. Intravenous fluids should be restricted prior to extrication.
   □ B. Acidification of the urine abolishes the risk of renal failure.
   □ C. A delay in fluid resuscitation increases the incidence of renal failure.
   □ D. Rhabdomyolysis occurs in fewer than 1 in 1000 victims of crush injury.

9. Which of the following is an indication for renal replacement therapy in patients with rhabdomyolysis?
   □ A. Persistent metabolic alkalosis.
   □ B. Hyperkalemia refractory to pharmacologic interventions.
   □ C. Myoglobin removal.
   □ D. Severe hypocalcemia.

10. In a patient with a myopathy who develops cardiac arrest after administration of succinylcholine, which of the following therapies should be initiated FIRST?
    □ A. Administration of intravenous calcium.
    □ B. Hemodialysis.
    □ C. Administration of furosemide.
    □ D. Lower extremity fasciotomy.

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CORRECT ANSWERS TO LESSON 26, VOLUME 36 (McGOLDRICK)