Rhabdomyolysis

A practical approach to diagnosis and management.

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Rhabdomyolysis is a descriptive term used in reference to striated muscle breakdown with subsequent leakage of cellular content into the circulation. Once released into the bloodstream, muscle cellular components (eg, myoglobin, creatine kinase, phosphate, and potassium) induce a cascade of reactions, resulting in end-organ damage. Renal failure may be caused by tubular obstruction, tubular necrosis, or renal vasoconstriction. It is estimated that 15% to 33% of individuals with rhabdomyolysis develop acute renal failure.

Clinically, the defining features of rhabdomyolysis include a triad of myalgia, weakness, and myoglobinuria. The biochemical hallmark of rhabdomyolysis is an elevation of serum creatinine kinase (CK), at least 5 times the upper limit of normal. Presentations range from asymptomatic to severe myalgias, limb weakness, and fulminant renal failure requiring dialysis.

The incidence of rhabdomyolysis is difficult to estimate, because some cases may be mild, and not everyone presents for medical attention. Hospital admissions secondary to rhabdomyolysis over a 7-year period were reported as 0.074% of all admissions. Other estimates are provided by studies of specific causes of rhabdomyolysis, rather than rhabdomyolysis as a whole. For example, the incidence of exertional rhabdomyolysis is reported as 22.2 cases per 100,000 per year.

### Etiologies

Although there are multiple approaches to categorizing etiologies of rhabdomyolysis, in clinical practice it is useful to separate these into exertional vs nonexertional (Table). Extreme physical activity may cause exertional rhabdomyolysis in otherwise healthy individuals. People with underlying myopathies (eg, mitochondrial disorders, metabolic diseases, and muscular dystrophies) subjected to an additional stressor may also develop exertional rhabdomyolysis. Nonexertional causes include drugs, toxins, inflammatory or autoimmune disease, infections, metabolic derangements, and direct muscle trauma. Muscle compression during prolonged immobility (eg, from stroke, after surgery, or because of altered consciousness after drug/alcohol intoxication) is a common frequent cause for rhabdomyolysis.

### TABLE. RHABDOMYOLYSIS ETIOLOGIES

| Nonexertional nontraumatic |  |
|----------------------------|  |
| Alcohol and recreational drugs: ethanol, methanol, narcotics, amphetamines, lysergic acid |  |
| Electrolyte disturbances: hypo- or hypernatremia, hypo- or hyperkalemia, hypophosphatemia, hypocalcemia |  |
| Endocrine disorders: hypo- or hyperthyroidism, hyperglycemic states |  |
| Environmental toxins: snake venom, spider venom, carbon monoxide |  |
| Hypo- or hyperthermia |  |
| Inflammatory myopathies (rare presentation) |  |
| Medications: statins, fibrin acid derivatives, salicylates |  |
| Neuroleptic malignant syndrome |  |
| Nonexertional traumatic |  |
| Compartment syndrome |  |
| Crush injury |  |
| Electrical injury |  |
| Infections |  |
| Immobilization |  |
| Surgery |  |
| Exertional acquired |  |
| Extreme physical activity and exertion |  |
| Hyperkinetic state |  |
| Sickle cell disease or trait (strenuous exercise) |  |
| Seizure |  |
| Exertional genetic |  |
| Congenital myopathies: ryanodine receptor 1 (RYR1) deficiency |  |
| Disorders of lipid metabolism: carnitine palmitoyltransferas II (CPT2) deficiency, carnitine deficiency |  |
| Glycogenoses: myophosphorylase deficiency (McArdle’s disease), phosphofructokinase deficiency |  |
| Mitochondrial diseases |  |
| Muscular dystrophies: dystrophinopathies, limb-girdle muscular dystrophies |  |
**Pathophysiology**

Regardless of the initial mechanism of muscle injury, the final common pathway involves a rapid influx of calcium into myocyte cytoplasm and mitochondria. Normally, the sarcolemma maintains a low intracellular calcium concentration via a Ca\(^{2+}\)-Na\(^{+}\)exchanger, which is powered by a Na\(^{+}\)-K\(^{+}\) ATPase pump. Similarly, the sarcoplasmic reticulum relies on a Ca\(^{2+}\)-ATPase membrane pump. Both of these mechanisms require a constant supply of adenosine triphosphate (ATP). 

Trauma can cause rupture of the sarcolemma, resulting in passive calcium diffusion intracellularly. Alternatively, the depletion of ATP—whether from intense exercise, sustained muscle contraction, or electrolyte derangement—can induce Na\(^{+}\)-K\(^{+}\) ATPase dysfunction, reversing the Na\(^{+}\)-Ca\(^{2+}\) exchanger and thereby depolarizing the sarcolemma. A disrupted sarcolemma, in turn, can promote further calcium secretion from the sarcoplasmic reticulum.

Ultimately, increased intracellular calcium concentration activates calcium-dependent proteases and phospholipases, leading to muscle fiber necrosis and release of intracellular contents into the circulation.

**Clinical Presentation**

The classic presentation of rhabdomyolysis includes myalgias; weakness; dark red or brown urine; elevated serum CK; and, in more severe cases, renal failure. The full triad of myalgia, muscle weakness, and pigmenturia, however, is seen only in 10% of cases. Elevated CK is typically seen within 2 to 12 hours and often peaks within 3 days, but elevated CK alone does not necessarily mean rhabdomyolysis has occurred. Some degree of hyperCKemia is not uncommon in the context of high-intensity exercise (eg, CK levels can be 22 times the upper limit of normal in male marathon runners after a race). Levels of CK that lead to renal failure are not well established; some studies suggest values as low as 5000 U/L are sufficient to cause renal failure. Rhabdomyolysis becomes clinically significant when CK elevation is sufficiently high to cause end-organ damage, such as renal failure.

Neurologists are often called on to determine if someone with rhabdomyolysis harbors an underlying myopathy. This distinction is critical, because it informs counselling for future activity levels and other important aspects of management (Figure). Several important clues raise suspicion for an underlying myopathy. Recurrent episodes of rhabdomyolysis, including recurrent episodes of pigmenturia, are suggestive of muscle disease. The circumstances triggering rhabdomyolysis, such as a viral illness or fasting, may also indicate the presence of an inherited myopathy. A family history of rhabdomyolysis may also indicate presence of an inherited myopathy. The degree and duration of CK elevation can also be helpful when considering the differential diagnosis. Levels of CK more than

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**Features of Rhabdomyolysis**

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated serum CK</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Myoglobinuria</td>
<td>Muscle tenderness</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>Swelling</td>
</tr>
<tr>
<td></td>
<td>Pigmenturia</td>
</tr>
</tbody>
</table>

**Can extrinsic factor be identified?**

Electrolyte derangement?  
Endocrine abnormalities?  
Toxic agent?  
Drugs (prescribed or recreational)?  
Trauma?

If no, Ongoing monitoring. If yes, Additional features?

Hyper-elevated CK?  
Persistently elevated CK?  
Family history significant?  
Prior episodes (pigmenturia or rhabdomyolysis)?  
Persistent weakness between episodes?  
Systemic features of autoimmune disease?

If yes, No further investigations. If no, Myopathy Workup:

Resting lactate  
Acylcarnitine profile  
Forearm exercise test  
Muscle biopsy  
EMG/NCS  
Genetic testing

Figure. Diagnostic algorithm for suspected rhabdomyolysis. 
Abbreviations: CK, creatinine kinase; EMG, electromyography; NCS, nerve conduction studies.

50 times the upper limit of normal at initial presentation suggests a metabolic disorder. A continued CK elevation for more than 8 weeks should raise suspicion for myopathy. 

The clinical picture beyond the acute phase is also extremely important. Individuals with persistent muscle
weakness in between distinct episodes are more likely to have a primary myopathy.

**Diagnostic Studies**

The diagnostic approach to rhabdomyolysis needs to be tailored to the suspected etiology. An initial common pathway, however, can be followed for all cases. Elevated serum CK may be the only indication of rhabdomyolysis in subclinical cases. Myoglobinuria is visible only when more than 100 g of muscle has been destroyed. The half-life of myoglobin is 2 to 4 hours, and it is excreted into the urine only when it overwhelms the serum protein-binding capacity.

These features make myoglobinuria a reliable marker only in the hyperacute phase of rhabdomyolysis.

Detection of an electrolyte derangement (eg, hypokalemia, hypophosphatemia, and hyper- or hyponatremia), which can be either a trigger or a consequence of rhabdomyolysis, is essential. A drug and toxin screen is indicated if a clear exertional or traumatic etiology is not established by the clinical history. Similarly, an endocrine work up is required, especially in the presence of an unexplained electrolyte derangement, with or without systemic features.

If the presentation suggests an underlying myopathy, additional investigations need to be considered. During the resting period, an elevated serum lactate can indicate the presence of an underlying mitochondrial myopathy. A nonischemic forearm exercise test can be used to diagnose McArdle’s disease. Mass spectrometry to determine an acylcarnitine profile can diagnose fatty acid oxidation disorders.

Muscle biopsy is an essential investigation for individuals with suspected myopathy who cannot be diagnosed with genetic testing. The timing of the biopsy is crucial because features of an inherited myopathy can be obscured by muscle necrosis during the acute phase of rhabdomyolysis. Electrodiagnostic testing (ie, EMG) can provide further support if the findings reveal myopathic features, although such testing should also be deferred until after the acute phase.

Genetic screening for inherited myopathies can be done via single gene testing, panel tests, targeted or whole exome sequencing, or mitochondrial genome testing. The choice of test depends on specific clinical features and the pattern of inheritance suggested by family history. Often, genetic testing can obviate the need for a muscle biopsy and EMG. For example, individuals with classic features of McArdle’s disease (eg, exercise intolerance, rhabdomyolysis, and second-wind phenomenon) can readily be diagnosed with genetic testing.

**Rhabdomyolysis and High-Intensity Exercise**

Recently, there has been a marked rise in the popularity of extreme conditioning programs (ECPs), such as CrossFit. These activities are characterised by high-intensity functional movements performed as a number of repetitions during a fixed time interval. There have been growing concerns regarding the overall safety of these programs, especially because some practitioners may be novice or inexperienced athletes. Overall, ECP-induced rhabdomyolysis has been reported in fit young individuals who are experienced athletes, in deconditioned athletes, and in novices. The incidence of serious complications such as acute renal failure as a result of exercise-induced rhabdomyolysis, however, is considerably lower than from other causes.

**Management**

Management of rhabdomyolysis should involve treatment of the renal and metabolic sequelae and an attempt to clarify the presence of any potential triggers or underlying precipitating conditions. Electrolytes must be checked frequently, and derangements corrected accordingly. If any drugs are identified as possible triggers, they should be promptly discontinued. The management of the renal complications is dependent on the severity of the injury and may involve diuresis with aggressive intravenous hydration or possibly dialysis. When possible, a nephrologist should be consulted. Urine output of more than 200 mL/hr is recommended as a target for hydration therapy. Routine use of urinary alkalinisation, with mannitol or sodium bicarbonate, has not been shown effective in preventing renal failure.

Admission to an intensive care unit for close monitoring may be required if there are significantly elevated CK levels or evidence of end-organ damage.

There are currently no clear guidelines on returning to exercise after an episode of rhabdomyolysis. A risk stratification approach has been suggested that classifies individuals as having high or low risk for recurrence. Factors associated with a high risk of recurrence include personal or family history of exertional rhabdomyolysis, persistent elevation in CK despite rest for 2 weeks, serum CK peak more than 100,000 UL, rhabdomyolysis complicated by acute kidney injury of any degree, and personal or family history of malignant hyperthermia. Those who are considered at high risk for recurrence are also more likely to have an underlying myopathy. For these individuals, a thorough work up is recommended including an EMG, laboratory investigations for metabolic disease, and possibly a muscle biopsy and/or genetic testing.

People who are considered at low risk of recurrence may return to exercise over 3 phases. Phase 1 consists of a 72-hour rest period with oral hydration in a thermally controlled environment. The CK level and urinalysis should be repeated at 72 hours. If these values are less than 5 times the upper limit of normal, then phase 2 can begin. In phase 2, the individual may do light exercise at their own pace. If this is well tolerated with no return of symptoms, then phase 3 can be commenced with a gradual return to regular sporting activities.
Summary

The clinical presentation of rhabdomyolysis is varied, and not all individuals exhibit the classic triad of weakness, myalgia, and myoglobinuria. Accurate diagnosis facilitates the prompt initiation of management, including removal of triggers and the correction of metabolic derangements. Although most cases of rhabdomyolysis are benign, some individuals harbor an occult myopathy. In selected cases further workup, including electrodiagnostic studies, muscle biopsy, and genetic testing is required.


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