Acute Pediatric Rhabdomyolysis — Treatment and Prevention

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Rhabdomyolysis is a serious condition due to muscles injury with subsequent releasing of their contents into the blood. It can lead to serious complications, such as electrolyte imbalance, acute renal failure, or disseminated intravascular coagulation. Direct injury and compression is the main cause of rhabdomyolysis, while others comprise excessive muscle use, statins, and hereditary cause. Elevation of creatinine kinase with myoglobinuria confirms the diagnosis. Management depends largely on the underlying etiology.

Definition of Acute Rhabdomyolysis

Rhabdomyolysis is a complex medical condition that is characterized by the rapid dissolution of damaged or injured skeletal muscle. The disruption of the skeletal muscle cell wall integrity leads to the release of key intracellular components, including creatine kinase, aldolase, lactate dehydrogenase, myoglobin, and electrolytes. The release of these intracellular products might be associated with electrolyte imbalances, acute renal failure, or disseminated intravascular coagulation.
In the past, it was difficult to estimate the incidence of rhabdomyolysis due to the lack of a formal and standard definition. In 2002, the American College of Cardiology, the American Heart Association, and the National Heart, Lung and Blood Institute jointly released a definition of rhabdomyolysis and other related conditions. The following table summarizes these definitions.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Myopathy</td>
<td>This is a general term that can refer to any form of muscle disease which can be acquired or inherited.</td>
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<tr>
<td>Myalgia</td>
<td>This term is reserved for muscle pain without a clinically significant elevation in serum creatine kinase.</td>
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<tr>
<td>Myositis</td>
<td>This term refers to muscle pain and weakness with creatine kinase elevation.</td>
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<tr>
<td>Rhabdomyolysis</td>
<td>Muscle symptoms with marked creatine kinase elevation, creatinine elevation, and myoglobinuria.</td>
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Rhabdomyolysis is responsible for approximately 15% of all adult cases of acute kidney injuries (AKI) in the USA. Over 26,000 patients are diagnosed with rhabdomyolysis in the USA each year. Rhabdomyolysis is most common in males and African-Americans. Rhabdomyolysis affects the patient in the age group of < 10 and 60 > years old.

It has been estimated that half of the children who develop acute rhabdomyolysis are going to develop AKI.

### Etiology of Acute Pediatric Rhabdomyolysis

#### Trauma-related direct injury or compression

Rhabdomyolysis can occur in patients secondary to crush injuries. These patients are prone to developing acute kidney injury due to extensive myoglobin release, thus requiring hemodialysis. *Crush injuries can occur due to earthquakes, mine accidents, motor/train accidents, building collapse, and bombings*, etc. Road traffic accidents are the most common cause of rhabdomyolysis, causing direct injury to the muscles. *Acute renal failure* (ARF) could result due to mechanical obstruction of renal tubules by myoglobin.

Prolonged immobilization arising out of hospitalization, paralysis, stroke, or long-duration surgeries also cause rhabdomyolysis due to prolonged compression. Although 1 hour of continuous compression is considered sufficient, even compressions lasting 20 minutes can cause rhabdomyolysis.

#### Muscular over-exertion and exercise-related injuries

Marathon runners, athletes and workers prone to excessive muscular exertion and exercises are at a higher risk of developing rhabdomyolysis. *Excessive muscle activity can result in muscle damage and rhabdomyolysis*. Patients who are affected by electrical injuries are also prone to develop this condition primarily due to continuous muscular contraction (tetany) and also due to direct electricity-related muscular injury (lightning strikes or electrocution). Seizures and alcohol withdrawal syndrome are associated with muscular exertion injury.
Inherited enzyme disorders and metabolic diseases

Inherited enzyme disorders and metabolic diseases that cause rhabdomyolysis include McArdle’s disease (glycogen storage disease type V, myophosphorylase deficiency, autosomal recessive), Tarui disease (glycogen storage disease type VII, phosphofructokinase deficiency, autosomal recessive), and phosphoglyceromutase deficiency. These patients are usually not aware of the disease and are usually diagnosed after admission to the hospital.

Statins and Rhabdomyolysis

Since the introduction of statins, many reports have pointed towards an association between the use of statins and rhabdomyolysis. The main risk factors for statin-induced rhabdomyolysis can be classified into endogenous and exogenous risks.

The endogenous risk factors for statin-induced rhabdomyolysis include age above 80 years, renal dysfunction, hepatic dysfunction, hypothyroidism, hypertriglyceridemia, and metabolic muscle diseases.

The exogenous risk factors can be summarized in the following:

- Alcohol consumption
- Heavy exercise
- The use of fibrates, nicotinic acid, cyclosporine, macrolide antibiotics, azole antifungals, verapamil, amiodarone, warfarin, and the consumption of more than 1 quart of grapefruit juice per day

Other causes

Muscle hypoxia due to major artery occlusion can be associated with muscle damage and rhabdomyolysis. Malignant hyperthermia, heat stroke, hypothermia and neuroleptic malignant syndrome can cause rhabdomyolysis.

Other causes of rhabdomyolysis include the abuse of alcohol, amphetamine, methadone, LSD, heroin, and cocaine. These substances may lead to rhabdomyolysis due to:

- The direct effect on the muscle tissue
- Prolonged compression following intoxication, seizures, muscular hyperactivity, and
- Prolonged immobilization causing muscle hypoxia.

Raver’s hematuria is reported in individuals who indulge in prolonged dancing leading to the development of rhabdomyolysis, especially with a history of amphetamine consumption.

Delirium tremens associated with alcohol withdrawal may also cause rhabdomyolysis. Patients with sickle-cell anemia are prone to develop rhabdomyolysis condition at high altitudes.

The following drugs can cause rhabdomyolysis:

- Salicylates
- Fibric acid derivates (bezafibrate, clofibrate, fenofibrate, gemfibrozil)
- Antipsychotics (haloperidol, fluphenazine, perphenazine, chlorpromazine)
- Corticosteroids
- **Antibiotics** (fluoroquinolones, pyrazinamide, trimethoprim/sulphonamide)
- Amphotericin B
- Itraconazole
- Zidovudine
- Benzodiazepines
- Antihistamines

Viral infections (influenza A and B, Epstein-Barr virus, Cytomegalovirus and **Human Immunodeficiency Virus** (HIV)) account for approximately one-third of all pediatric rhabdomyolysis cases. The relation between viral infections and rhabdomyolysis is not clear.

Snake bites, spider venom, CO (carbon monoxide), Tricholoma equestre (mushroom), etc. are also reported to cause rhabdomyolysis.

Rhabdomyolysis can be caused by **electrolyte imbalances**, including hypokalemia, hypophosphatemia, hypocalcemia, and hypo- or hypernatremia. Hyperaldosteronism, hypothyroidism, and diabetic ketoacidosis are among the most common endocrinological causes of rhabdomyolysis. Autoimmune causes of rhabdomyolysis include dermatomyositis and polymyositis.

### Pathophysiology of Acute Pediatric Rhabdomyolysis

Despite the etiology, the pathophysiology of rhabdomyolysis is more or less consistent.

**Note:** Generally, the channels and ion pumps located on sarcolemma maintain a high K⁺ concentration and low Na⁺ and Ca²⁺ concentrations within the cell. Rhabdomyolysis-related damage to the sarcolemma or shortage of energy (ATP) can lead to dysfunction of the ion channels and pumps, resulting in increased calcium influx into the cell. This, in turn, activates calcium-dependent phospholipases and proteases, leading to destructions of the structural proteins. Following the cellular destruction, several cellular components and proteins (myoglobin, creatine kinase, aldolase, and lactate dehydrogenase) enter the circulation, damages capillaries and causes leakage and edema.

Myoglobin is the oxygen-carrying protein present in the skeletal muscle and is usually bound to plasma proteins. **In rhabdomyolysis, the myoglobin levels exceed the binding capacity of the plasma proteins**, leading to unbound myoglobin in the circulation. This free myoglobin can cause acute kidney injury via different mechanisms.

**Note:** Most importantly, free myoglobin is precipitated in the glomerular filtrate and causes mechanical obstruction of the tubules. Hyperuricemia and intraluminal cast formation also contribute to acute renal involvement. Intraluminal cast formation occurs when myoglobin binds to the Tamm-Horsfall protein, especially in the presence of acidic urine. Additionally, hypovolemia, vasoconstriction, and direct deleterious effect of myoglobin on the renal tissue also contribute to the acute kidney injury in rhabdomyolysis.
Symptoms and Signs of Acute Pediatric Rhabdomyolysis

Approximately 50% of rhabdomyolysis patients present with the classic triad of symptoms that include myalgia, weakness, and dark tea or cola colored urine. However, these classical symptoms may be absent in the other 50% of the patients. These symptoms are non-specific and a firm diagnosis cannot be made on these findings.

Usually, a history of medication intake, trauma, or alcohol/drug abuse is associated. The patients may also present with features of acute kidney injury. The mortality rate is high in patients with rhabdomyolysis complicated by acute kidney injury, especially in the presence of a high creatine kinase level.

Muscle weakness is seen, especially in the proximal leg. Severe hyperkalemia and hypocalcemia can cause cardiac arrhythmias. Compartment syndrome may be present, especially in the lower limbs. During fluid resuscitation, the edema of the lower limbs may get worse. The intracellular components released into the circulation may activate the coagulation pathway, leading to disseminated intravascular coagulation in a few cases.

Patients with McArdle’s disease (glycogen storage disease type V) experience a second-wind phenomenon. On taking a short rest following strenuous exercise, these patients develop enhanced exercise tolerance due to the release of hepatic glucose.

Diagnosis of Acute Pediatric Rhabdomyolysis

Apart from a history and clinical examination, the diagnosis of rhabdomyolysis is based on the finding that the serum creatine kinase is elevated more than five-fold the upper limit of the normal range. A creatine kinase test is the most reliable and sensitive indicator of kidney damage. Creatine kinase (CK-MM subtype) usually starts increasing 2—12 hours after the muscle injury, peaks at 24 hours, and returns to baseline values in 3—5 days. A level of creatine kinase above 15,000 U/L indicates renal damage and renal
failure.

Also, the urine dipstick turns positive for blood, although there are no red blood cells in the urine. Myoglobinuria is clinically evident only if the urine myoglobin levels exceed 100 mg/dL.

If malignant hyperthermia is suspected alongside rhabdomyolysis, genetic testing for **RYR1 mutation or, additionally a caffeine contracture test** may be performed. Genetic testing is required if an inherited enzyme deficiency is suspected. Lipin-1 (LPIN-1) gene mutations cause recurrent rhabdomyolysis in children. This gene codes for muscle-specific phosphatidic acid phosphatase. The episodes of rhabdomyolysis are precipitated by fever, sepsis or infections, prolonged fasting, or exercise.

Metabolic disturbances such as hyperkalemia, if present, require an electrocardiogram for further cardiac evaluation. Hypocalcemia may be present in an initial stage, while a **rebound hypercalcemia is observed during the correction stage**.

**Differential Diagnosis**

Other conditions with elevated creatine kinase include myositis, muscular dystrophies, hyperthyroidism, and hypothyroidism. A muscle biopsy may be used to differentiate rhabdomyolysis from myositis.

Other causes of dark-colored urine include porphyria, hemoglobinuria, rifampicin or vitamin B12, and beetroot.

**Treatment and Management of Acute Pediatric Rhabdomyolysis**

**Intravenous fluid administration**

It is of paramount importance to **initiate early treatment in order to prevent further renal damage**. There may be substantial hypovolemia due to the accumulation of fluid in the affected muscles; hence, emergent intravenous fluid administration (0.9 % NaCl, 1.5 L/hour) is indicated to counter the hypovolemia and prerenal azotemia.

**Fasciotomy**

If the patient is taking any drug that could cause rhabdomyolysis, it should be stopped and, if required, appropriate antidotes should be administered. In patients with **compartment syndrome, fasciotomy should be considered** early to prevent further renal and muscular damage.

**Hyperkalemia and hypercalcemia treatment**

Dyselectrolytemias should be corrected. Hyperkalemia is treated with insulin, glucose, and sodium bicarbonate. Hypocalcemia should be treated only if there is associated hyperkalemia. The mainstay of acute kidney injury management in this condition is **fluids and hydration therapy (aggressive)**. A urine output of 200 mL/h should be maintained until the plasma levels of creatine kinase drop below 1000 U/L.
Hemodialysis

Hemodialysis may be required in 4—8 % of patients with rhabdomyolysis. Most frequent indications for hemodialysis in this condition are severe hyperkalemia and persistent oligo-anuric renal failure. However, continuous venovenous hemofiltration works better than hemodialysis to filter out larger molecules like myoglobin.

Prevention

In patients with inherited susceptibility to develop rhabdomyolysis, prevention is the best modality of management. A low-fat diet may be helpful. Other dietary measures may be taken, depending on the underlying condition. In patients with malignant hyperthermia, caution should be taken while administering anesthetic agents. Prolonged exercise or fasting should be avoided in patients with glycogen storage disorders and fatty acid oxidation disorders.

Progression and Prognosis of Acute Pediatric Rhabdomyolysis

The prognosis largely depends on when the management was instituted during the course of the disease. Patients who are treated early in an aggressive manner have a very good prognosis. The prognosis is markedly worse if there is an associated acute kidney injury. In children, the mortality rate due to rhabdomyolysis ranges from 7—10 %; however, almost all children succumb to the underlying etiology of rhabdomyolysis (trauma, sepsis, burns, or toxicity).

Review Questions

The correct answers can be found below the references.

1. Which of the following is the most common cause of rhabdomyolysis (adult and pediatric combined)?
   A. Road traffic accidents
   B. Alcohol intoxication
   C. Inherited enzyme disorders
   D. Malignant hyperthermia
   E. Prolonged exercise

2. Which of the following factors markedly worsens the prognosis in patients with rhabdomyolysis?
   A. Anemia
   B. Leucocytosis
   C. Creatine kinase more than 1000 U/L
   D. Fever
   E. Acute kidney injury

3. A 14-year-old boy was brought to the emergency department with myalgia, weakness, cola-colored urine, and a crush injury to his left leg following a road traffic accident. His creatine kinase levels were 12,000 U/L. Which is the most appropriate initial management for this patient?
A. Observation for spontaneous resolution
B. Analgesics and antibiotics
C. Urgent left leg amputation
D. Adequate intravenous fluid administration
E. Cystoscopy

References


Correct answers: 1A, 2E, 3D

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