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Rhabdomyolysis: Etiology, Pathophysiology, Clinical Features, Diagnosis, and Management

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Abstract

Rhabdomyolysis is a potentially life-threatening condition characterized by the breakdown of skeletal muscle fibers and the release of intracellular components, including myoglobin, creatine kinase, potassium, and phosphate, into the circulation. Its clinical spectrum ranges from mild biochemical abnormalities to severe complications such as acute kidney injury, electrolyte disturbances, disseminated intravascular coagulation, and cardiac arrhythmias. Early recognition and treatment are essential for improving outcomes. The causes of rhabdomyolysis are diverse and can be broadly classified as traumatic, exertional, toxic, metabolic, infectious, and genetic. Traumatic causes include crush injuries, burns, and prolonged immobilization. Exertional rhabdomyolysis is increasingly reported in athletes and military personnel following intense physical activity, especially in the setting of dehydration or heat stress. Drugs and toxins, such as statins, alcohol, and illicit substances, may produce direct muscle toxicity. Metabolic and electrolyte disorders, infections, and inherited metabolic myopathies can also impair muscle cell stability and energy metabolism, leading to muscle injury. At the cellular level, damage to the muscle membrane results in increased intracellular calcium, activation of proteolytic enzymes, and muscle necrosis, with subsequent release of myoglobin and creatine kinase. Myoglobin contributes to acute kidney injury through tubular obstruction and direct nephrotoxicity, particularly in the presence of hypovolemia. Clinical manifestations are often nonspecific, and the classic triad of muscle pain, weakness, and dark urine is uncommon. Diagnosis relies mainly on markedly elevated creatine kinase levels and myoglobinuria. Treatment is primarily supportive, with early aggressive intravenous fluid administration to prevent renal complications. Prognosis depends on injury severity and prompt management.

Keywords: Creatine kinase; Hydration; Kidney injury; Muscle pain; Myoglobin.

Abbreviation: **AKI:** Acute Kidney Injury

Introduction

Rhabdomyolysis is a potentially life-threatening clinical syndrome resulting from skeletal muscle breakdown and the subsequent release of intracellular constituents, including myoglobin, creatine kinase, potassium, and phosphate, into the systemic circulation (1,2). The condition encompasses a broad clinical spectrum, ranging from asymptomatic biochemical abnormalities to severe complications such as acute kidney injury (AKI), electrolyte derangements, disseminated intravascular coagulation, and fatal cardiac arrhythmias (2). Early diagnosis and prompt initiation of therapy are critical determinants of outcome (3).

The etiological factors contributing to rhabdomyolysis are diverse and multifactorial. These causes may be broadly categorized into traumatic, exertional, toxic, metabolic, infectious, and genetic origins. A comprehensive classification of these etiologies, along with their underlying mechanisms, is presented in Table 1.

Traumatic and mechanical causes, including crush injuries, prolonged immobilization, electrical trauma, and severe burns, result in direct muscle cell damage and ischemia (2). Exertional and heat-related rhabdomyolysis is increasingly recognized among athletes and military personnel following strenuous or unaccustomed physical activity, particularly in the presence of dehydration or hyperthermia (4). Numerous drugs and toxins, such as statins, alcohol, cocaine, and amphetamines, exert direct myotoxic effects or induce vasoconstriction and hyperthermia, thereby precipitating muscle injury (1,3).

Metabolic and electrolyte abnormalities impair muscle energy metabolism and membrane stability, predisposing muscle fibers to necrosis (2). Infectious causes include viral and bacterial pathogens that induce muscle injury through direct invasion, toxin production, or cytokine-mediated inflammation (1,5). Inherited metabolic myopathies, summarized in Table 1, are an important cause of recurrent rhabdomyolysis, particularly in younger individuals (4).

Table 1. Etiological classification of rhabdomyolysis.

Category	Specific Causes	Mechanism of Muscle Injury
Traumatic/ Mechanical	Crush injuries, prolonged immobilization, electrical injury, burns	Direct muscle destruction, ischemia, membrane disruption
Exertional/ Heat-related	Strenuous exercise, heat stroke, dehydration, military training	ATP depletion, hyperthermia, increased sarcolemmal permeability
Drugs & Toxins	Statins, alcohol, cocaine, amphetamines, heroin, antipsychotics	Direct myotoxicity, vasoconstriction, hyperthermia
Metabolic/ Electrolyte	Hypokalemia, hypophosphatemia, hypothyroidism, diabetic ketoacidosis	Impaired muscle energy metabolism
Infectious	Influenza, HIV, COVID-19, sepsis (*Staphylococcus, Legionella*)	Cytokine-mediated injury, toxins, hypoxia
Genetic/ Inherited	McArdle disease, fatty acid oxidation defects, mitochondrial myopathies	Enzyme deficiencies causing recurrent muscle breakdown

The pathophysiology of rhabdomyolysis involves a sequence of cellular and systemic events, outlined in Table 2. Initial disruption of the sarcolemmal membrane leads to uncontrolled calcium influx into myocytes, activating proteolytic enzymes and phospholipases that degrade intracellular structural proteins (1,2). This process culminates in muscle cell necrosis and the release of creatine kinase and myoglobin into the circulation.

Myoglobin plays a central role in the development of AKI. It is filtered by the glomeruli and precipitates within renal tubules, particularly under acidic conditions, causing tubular obstruction and direct nephrotoxicity (3). Concurrent hypovolemia and renal vasoconstriction further exacerbate renal injury, emphasizing the importance of early volume resuscitation (2).

Table 2. Pathophysiological events in rhabdomyolysis.

Step	Pathophysiological Process	Clinical Consequence
1	Sarcolemmal membrane disruption	Leakage of intracellular contents
2	Increased intracellular calcium	Activation of proteases and phospholipases
3	Muscle cell necrosis	Release of creatine kinase and myoglobin
4	Myoglobin filtration by kidneys	Tubular obstruction
5	Renal vasoconstriction + hypovolemia	Acute kidney injury
6	Electrolyte release (K^+, PO_4^{3-})	Arrhythmias, metabolic derangements

The clinical presentation of rhabdomyolysis is highly variable. The classic triad of muscle pain, weakness, and dark-colored urine is present in fewer than 10% of cases (1). More commonly, patients present with nonspecific symptoms such as muscle tenderness, swelling, fatigue, fever, nausea, and vomiting. The full range of clinical features across organ systems is summarized in Table 3.

Table 3. Clinical features of rhabdomyolysis.

System	Manifestations
Musculoskeletal	Muscle pain, tenderness, swelling, weakness
Renal	Dark-colored urine, oliguria, acute kidney injury
Systemic	Fever, fatigue, malaise
Gastrointestinal	Nausea, vomiting
Neurological/ Cardiac	Confusion, arrhythmias due to electrolyte imbalance

Renal manifestations, including oliguria and dark urine due to myoglobinuria, often signal severe disease. Neurological and cardiac symptoms may occur secondary to electrolyte disturbances, particularly hyperkalemia, which can result in life-threatening arrhythmias (2,3).

Laboratory investigations are central to the diagnosis of rhabdomyolysis. The characteristic biochemical abnormalities are detailed in Table 4. Serum creatine kinase is the most sensitive diagnostic marker typically exceeding five times the upper limit of normal and frequently reaching levels greater than 100,000 IU/L in severe cases (1,5). Urinalysis commonly reveals a positive dipstick test for blood in the absence of red blood cells, reflecting the presence of myoglobin (2).

Table 4. Laboratory findings in rhabdomyolysis.

Investigation	Typical Findings	Clinical Significance
Creatine kinase	>5,000 IU/L (often >100,000 IU/L)	Diagnostic marker
Urinalysis	Positive blood, no red blood cells	Indicates myoglobinuria
Serum potassium	Elevated	Risk of cardiac arrhythmias
Serum phosphate	Elevated	Marker of muscle breakdown
Serum calcium	Low (early), high (recovery phase)	Reflects calcium shifts
Serum creatinine	Elevated	Acute kidney injury
Arterial blood gas	Metabolic acidosis	Severe muscle injury

Electrolyte abnormalities, including hyperkalemia, hyperphosphatemia, and early hypocalcemia, are common and contribute significantly to morbidity (3). Renal function tests may demonstrate rising creatinine levels, indicating AKI.

The management of rhabdomyolysis is primarily supportive and aims to prevent complications, particularly AKI. Key management strategies are summarized in Table 5. Early and aggressive intravenous fluid resuscitation with isotonic saline remains the cornerstone of therapy, with the goal of maintaining urine output at 200-300 mL per hour (1,2).

Table 5. Management of rhabdomyolysis.

Aspect	Intervention	Rationale
Initial treatment	Aggressive IV isotonic fluids	Prevents myoglobin-induced acute kidney injury
Urine output goal	200-300 mL/hour	Enhances renal clearance
Electrolyte correction	Treat hyperkalemia urgently	Prevents arrhythmias
Avoid nephrotoxins	Stop NSAIDs, contrast agents	Reduces renal injury
Dialysis	If acute kidney injury, refractory hyperkalemia, acidosis	Life-saving intervention
Treat underlying cause	Stop drugs, treat infection, cooling	Prevents recurrence

Electrolyte disturbances require close monitoring and prompt correction, especially hyperkalemia due to its arrhythmogenic potential (3). Nephrotoxic agents should be avoided, and renal replacement therapy is indicated in cases of refractory electrolyte abnormalities, severe acidosis, or volume overload (2,5). Identification and treatment of the underlying cause are essential to prevent recurrence.

Despite appropriate therapy, rhabdomyolysis may lead to several serious complications, summarized in Table 6. AKI is the most common and clinically significant complication, accounting for increased mortality and prolonged hospitalization (2). Other complications include compartment syndrome, disseminated intravascular coagulation, metabolic acidosis, and fatal cardiac arrhythmias (3,4).

Table 6. Complications of rhabdomyolysis.

Complication	Pathogenesis	Clinical Impact
Acute kidney injury	Myoglobin nephrotoxicity	Most serious complication
Hyperkalemia	Release from damaged muscle	Fatal arrhythmias
Metabolic acidosis	Lactic acid accumulation	Hemodynamic instability
Hypocalcemia/ Hypercalcemia	Calcium redistribution	Neuromuscular symptoms
Compartment syndrome	Muscle edema	Requires urgent fasciotomy
Disseminated intravascular coagulation	Severe systemic inflammation	Bleeding, organ failure

The prognosis of rhabdomyolysis largely depends on the severity of muscle injury, the presence of complications, and the timeliness of treatment. With early recognition and adequate management, most patients experience complete recovery (1). Delayed intervention is associated with increased risk of permanent renal damage and death (2,5).

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Conflicts of interest

No conflict of interest.

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