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Review

An evidence-based narrative review of the emergency department evaluation and management of rhabdomyolysis

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ABSTRACT

Background: Rhabdomyolysis is a medical condition caused by muscle breakdown leading to potential renal damage. This can result in significant morbidity and mortality if not rapidly identified and treated.
Objective: This article provides an evidence-based narrative review of the diagnosis and management of rhabdomyolysis, with focused updates for the emergency clinician.
Discussion: Rhabdomyolysis is caused by the breakdown of muscle cells leading to the release of numerous intracellular molecules, including potassium, calcium, phosphate, uric acid, and creatinine kinase. There are a number of potential etiologies, including exertion, extreme temperature changes, ischemia, infections, immobility, drugs, toxins, endocrine causes, autoimmune reactions, trauma, or genetic conditions. Findings can include myalgias, muscle weakness, or dark-colored urine, but more often include non-specific symptoms. The diagnosis is often determined with an elevated creatinine kinase greater than five times the upper-limit of normal. Severe disease may result in renal failure, electrolyte derangements, liver disease, compartment syndrome, and disseminated intravascular coagulation. Treatment includes addressing the underlying etiology, as well as aggressive intravenous hydration with a goal urine output of 300 mL/h. Bicarbonate, mannitol, and loop diuretics do not possess strong evidence for improved outcomes. Renal replacement therapy should be determined on a case-by-case basis. Most patients are admitted, though some may be appropriate for discharge.
Conclusion: Rhabdomyolysis is a potentially dangerous medical condition requiring rapid diagnosis and management that may result in significant complications if not appropriately identified and treated. Emergency clinician knowledge of this condition is essential for appropriate management.

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1. Introduction

1.1. Background

Rhabdomyolysis is a complex condition existing along a spectrum, which is defined by the breakdown of damaged muscle and release of intracellular muscle content, including myoglobin, creatine kinase (CK), lactate dehydrogenase, and electrolytes [1–6]. The disease ranges from asymptomatic with mild CK elevation to a life-threatening condition with renal failure, severe electrolyte derangements, and disseminated intravascular coagulation (DIC) [1,2,7–10]. Rhabdomyolysis can be classified by several means including mechanism of injury, exertional versus non-exertional, and acquired versus inherited [1,5,11].

The true frequency of rhabdomyolysis is difficult to determine, as there are no prospective studies assessing the incidence of rhabdomyolysis, and many mild cases are not recognized or reported. In the United States, approximately 26,000 cases are reported annually [1,2,9–13]. One study conducted in a university hospital over a 7-year period found a 0.074% prevalence of a CK > 5000 international units/Liter (IU/L) in their population [14], while another study in military trainees found 22.2 cases per 100,000 people annually [15]. For pediatric patients, one study reported 4 cases per 1500 patients over a one-year period [16]. Overall, rhabdomyolysis is more common among African-Americans, males, patients aged <10 and >60 years, and those with a body mass index > 40 kg/m^2 [11,17,18]. The overall recurrence rate of the disease is not known. However, recurrence rates for exertional rhabdomyolysis range from 0.08% to 11%, though this may be higher in patients with genetic or muscular disorders [15,19,20].

1.2. Methods

The authors searched PubMed and Google Scholar for articles using a combination of the keyword and Medical Subject Heading "rhabdomyolysis" for production of this narrative review, including case reports

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and series, retrospective and prospective studies, systematic reviews and meta-analyses, and narrative reviews. The literature search was restricted to studies published in English. Authors decided which studies to include for the review by consensus. Initial literature search revealed over 300 articles. A total of 82 articles were selected for inclusion in this review, focusing on emergency department evaluation and management of rhabdomyolysis. Most of the available data come from retrospective studies and case reports, with limited prospective data. As this is a narrative review, authors did not pool individual study data. Authors did not specifically evaluate crush syndrome in this review article.

2. Discussion

2.1. Anatomy and pathophysiology

Rhabdomyolysis results from a direct injury to muscle cells, known as myocytes, leading to reduced energy supply to the cell [1,2,21-25]. Normal myocyte physiology is regulated by Na^+/K^+ and Na^+/Ca^{2+} pumps on the plasma membrane of myocytes that maintain low intracellular concentrations of Na^+ and Ca^{2+} and high concentrations of K^+ [2,22-27]. In a normal myocyte, cell depolarization causes Ca^{2+} to flood into the cytoplasm, resulting in actin-myosin cross-linking and contraction [1,2,22-24]. This process relies on sufficient energy from adenosine triphosphate (ATP), and any disruption of the ion channels or reduced ATP will result in an electrolyte imbalance and increased cellular permeability [2-4,22]. Muscle injury or decreased ATP resulting in cell wall destruction causes an influx of Na^+ and Ca^{2+}, increasing water content and destroying cellular attachments [2-4,22]. The high Ca^{2+} levels can result in prolonged muscle contraction, resulting in further ATP decreases, while the elevated Ca^{2+} levels also directly promote cell lysis [6,12,28-30]. These mechanisms result in an inflammatory myolytic cascade with myocyte necrosis, which releases muscle contents (including potassium, calcium, sodium, phosphate, myoglobin, CK) into the bloodstream and interstitial spaces [1-3,31]. Myoglobin normally functions as a carrier of oxygen in muscle. It is typically bound to plasma globulins in the blood and concentrates in the renal tubules [2-4,23,29,30]. In rhabdomyolysis, myoglobin levels exceed the blood's protein-binding capacity and, within the acidic environment, can precipitate and damage the kidneys through obstruction of the renal tubules, oxidative mechanisms, and direct vasoconstrictive effects [12,32,33]. Tamm-Horsfall protein is a glycoprotein produced in the thick ascending limb of the loop of Henle and is excreted in the urine. In rhabdomyolysis, this protein can precipitate, interact with myoglobin, and form granular casts, resulting in obstruction of renal tubules and renal injury [6,12,28–30,33]. This precipitation worsens in acidic urine. In the setting of reperfusion injury (e.g., acute ischemic limb compartment syndrome), ischemia-induced rhabdomyolysis may occur in a delayed fashion [1-5].

Key Point. Rhabdomyolysis is due to muscle breakdown releasing potassium, calcium, sodium, phosphate, myoglobin, and CK. This has a variety of potential consequences, including renal injury.

2.2. Etiologies

While traumatic injury or overexertion is a common cause of rhabdomyolysis, a variety of other etiologies have also been described, which include both inherited and acquired causes (Table 1) [1-5,17-20,25-28,33–35]. Approximately 75% of first-time episodes of rhabdomyolysis are due to an acquired cause [31,36,37], with 60% of patients possessing ≥2 risk factors [2]. In the United States, exercise/overexertion, drug intoxication, and immobility are responsible for a significant number of cases [3]. Multiple episodes of rhabdomyolysis, recurrent muscle cramps with exercise, and a positive family history of rhabdomyolysis and muscular or genetic disorders should raise the suspicion for an inherited underlying etiology of rhabdomyolysis [12,38–41]. Statin use may be associated with muscle soreness and rhabdomyolysis [9,1040,41]. Approximately 10% of patients on a statin medication will experience muscle pain or swelling, but the overall the risk of rhabdomyolysis is low in patients on a statin (1–2 patients for every 100,000 patients taking a statin) [9,10,40,41]. Statin-associated rhabdomyolysis occurs with greater frequency in older patients, who may be taking multiple higher-risk medications concurrently (see Table 1), and have a greater proportion of comorbidities (e.g., renal disease, cardiovascular disease, diabetes, hepatic disease) [9,10,40,41]. Exertional rhabdomyolysis possesses an incidence of 29.9 cases per 100,000 patient-years and is associated with a variety of exercises and sports including running, spinning, football, bodybuilding, and swimming, among others [42,43]. Hyperthermia, recent changes to the exercise routine, eccentric or extreme exercise, dehydration, sickle cell anemia, medications (e.g., non-steroidal anti-inflammatory medications), and preexisting disease (autoimmune or metabolic disorders) predispose athletes to exertional rhabdomyolysis [1–5,17–20,25-28,34-47].

Table 1
Etiologies of rhabdomyolysis [1-5,17-20,25-28,34-47].

Trauma or compression	Motor vehicle accidents, prolonged immobilization, crush syndrome, electrical injury, burns
Exertion	Intense exercise, seizure, status asthmaticus, sickle cell crisis, alcohol withdrawal
Extreme changes in body temperature	Serotonin syndrome, malignant hyperthermia, neuroleptic malignant syndrome, hyperthermia, hypothermia
Electrolyte alterations	Hypokalemia, hypophosphatemia, hypocalcemia, hyponatremia, hypernatremia, hyperglycemic states
Muscle ischemia/hypoxia	Artery occlusion due to embolus, thrombus, or during vascular surgery
Infections	Influenza, coxsackie, Epstein-Barr virus, herpes virus, HIV, *Salmonella*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Clostridium* species, *Legionella*, sepsis
Drugs and toxins	Statins, anti-lipid agents (ezetimibe, clofibrate, gemfibrozil), proton pump inhibitors, psychiatric medication (SSRIs, SNRIs, TCAs, benzodiazepines, barbiturates, phenothiazines, lithium), alcohol, cocaine, opiates, amphetamines, LSD, phencyclidine, synthetic cannabinoids, bath salts, antihistamines, propofol, arsenic, carbon monoxide, azathioprine, quinidine, salicylates, succinylcholine, thiazides, vasopressin, pentamidine, terbutaline, theophylline
Endocrine	Hyperthyroidism, hypothyroidism, hyperaldosteronism
Autoimmune	Dermatomyositis, polymyositis
Genetic	Lipid metabolism disorders, Krebs cycle disorders, mitochondrial chain disorders, G6PD deficiency, muscular dystrophies
Foodborne	Ingestion of burbot, eel, pike, crayfish, buffalo fish, and several other fish/crustacean species

HIV, human immunodeficiency virus; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitors; TCA, tricyclic antidepressants; LSD, lysergic acid diethylamide; G6PD, glucose-6-phosphate dehydrogenase.

2.3. History and physical examination

Disease presentation varies widely, ranging from asymptomatic to severe cases with end-organ damage, acute renal failure, DIC, and cardiac dysrhythmias [1-5,12,47-55]. The presentation reflects both the primary disease and associated symptoms from the complications (e.g., muscle injury, renal failure) [1-3]. When evaluating a patient with suspected rhabdomyolysis, clinicians should first obtain a focused history concerning symptoms of rhabdomyolysis, risk factors, family history of rhabdomyolysis, urine output and changes in color, and prior episodes of rhabdomyolysis. The conventional triad includes acute or subacute myalgias, transient muscle weakness, and darker-colored urine [1-4,7,27,31,49]. However, the presence of all three symptoms is found in <10% of patients with rhabdomyolysis [1-5,12]. Patients

often experience non-specific symptoms, which may include swelling, fever, weakness, palpitations, tachycardia, nausea, emesis, confusion, agitation, and oliguria or anuria [1,4,25]. The most common symptoms include muscle pain (>80%), weakness (>70%), and muscle swelling (8%) [56,57]. Muscle weakness typically includes the affected body part, with the proximal legs most frequently affected [1-5,7]. Pediatric patients more commonly complain of myalgias, fever, and a viral prodrome [35]. Urine findings are dependent on the patient's muscle mass, urine concentration, severity of the muscular injury, and renal function [12,21-24,50-52]. Dark-colored urine is described in <5% of cases and should not be relied upon to exclude the diagnosis [2,35].

Key Point. Though the classic triad includes acute or subacute myalgias, transient muscle weakness, and darker-colored urine, this occurs in only 10% of patients. The most common symptoms include muscle pain (>80%), weakness (>70%), and muscle swelling (8%), and nonspecific symptoms are common.

2.4. Diagnostic testing

Initial diagnostic testing should include an electrocardiogram (ECG), complete blood count (CBC), electrolytes (including calcium and phosphate), renal and liver function testing, CK, uric acid, and urinalysis [58,59]. Common metabolic derangements accompanying rhabdomyolysis can include hyperkalemia, hyponatremia, metabolic acidosis, hypo- or hypercalcemia, hyperphosphatemia, and hyperuricemia [3,4,22,51]. Due to the potential risk of hematologic abnormalities, a coagulation panel should be obtained in toxic-appearing patients [1-4]. Renal injury occurs in up to 50% of cases [52]. An elevated CK is diagnostic, with many experts using a threshold level of five times the upper-limit of normal or approximately 1000 IU/L. [3,4,6,11,58,59] CK levels typically increase 2–12 h after the injury, peak over 24–72 h, and decline gradually over 5–10 days [6,11,56]. It is important to note that baseline CK levels may be greater than five times the upper-limit of normal in patients with chronic muscle diseases (e.g., muscular dystrophy, inflammatory myopathies) [56]. In these patients, it can be valuable to compare their current CK level with their baseline values and correlate with clinical symptoms [39,56]. A meta-analysis suggests mean CK level and risk of acute kidney injury (AKI) may be correlated in the setting of crush injuries, but CK levels in the setting of rhabdomyolysis due to other causes are not predictive of AKI [11,51,60]. Serum myoglobin is not required routinely for patients with suspected rhabdomyolysis. It has a shorter half-life than CK (3 h versus 36 h) and can normalize within 6–8 h, resulting in a poor sensitivity that cannot reliably exclude rhabdomyolysis [4,59,61]. Myoglobin may be more valuable for assessing trends in the disease but can miss cases of rhabdomyolysis that present in a delayed fashion [59,62]. Data regarding myoglobin ability to predict AKI are inconclusive, and myoglobin should not be currently used to predict risk of AKI [4,11,51,61].

Due to the underlying pathophysiology, rhabdomyolysis can involve several other organ systems. Patients with severe disease may experience organ failure, which can lead to death in upwards of 8% of cases [1,4,12]. Renal failure may develop in 14% to 46% of patients with rhabdomyolysis, typically occurring due to acute tubular necrosis from myoglobin deposition and obstruction [1,2,7,12,36,47-55]. Urine pH demonstrates an inverse relationship with urine myoglobin precipitation: as urine pH decreases, myoglobin precipitation increases [4]. Hyperkalemia and hypocalcemia may result in cardiac dysrhythmia and death [12,24-26,47-50]. Liver dysfunction occurs in one quarter of cases and is likely multifactorial [1,7,8,49,54]. DIC occurs due to the systemic activation of the coagulation pathway from myocyte components [1,2,4].

Urinalysis may demonstrate the presence of moderate or large blood with few red blood cells on microscopy [3,11]. This is caused by myoglobin release, which is subsequently filtered through the urine resulting in a false positive urine blood reading. However, when assessed via a urine dipstick, this finding is only 41% sensitive for rhabdomyolysis and should not be used to exclude the diagnosis [62]. Alternatively, urinary myoglobin levels can be detected in small amounts (i.e., ≤5 μg/L) in many patients, but levels > 20 μg/L are suggestive of rhabdomyolysis [63,64]. Importantly, while an elevated urinary myoglobin is highly sensitive, it has poor specificity, ranging from 15% to 91% [61]. Data concerning urine myoglobin as a predictor of AKI in rhabdomyolysis are of low quality, though low myoglobin clearance may be suggestive of increased risk of AKI [4,61,65]. This requires further study before routine use.

Key Point. Diagnostic testing should include ECG, CBC, electrolytes, renal and liver function testing, CK, uric acid, and urinalysis. Serum myoglobin is not required for diagnosis and has poor sensitivity. Serum CK is a reliable means of diagnosis.

2.5. Treatment

Treatment should be targeted at both the underlying etiology and the consequent rhabdomyolysis [59]. If the etiology is temperature-related, active cooling or warming should be initiated. Compartment syndrome requires emergent fasciotomy, while arterial occlusions should receive thrombectomy or vascular intervention as indicated [1,2]. Infections should receive appropriate antibiotics, and all drug- or medication-related causes should have the medication discontinued and receive an appropriate antidote (antivenom for envenomation, fomepizole for toxic alcohol ingestion, etc.) if applicable [59].

Initial treatment for patients with confirmed rhabdomyolysis includes intravenous (IV) fluid rehydration, with a goal urine output of 300 mL/h, which may require an infusion up to 1.5 L/h of IV fluids [3,63,66,67]. However, in patients who are anuric, fluids can lead to interstitial or pulmonary edema and should be used cautiously [22]. Fluid selection may include either a balanced crystalloid (e.g., lactated Ringer's solution) or 0.9% normal saline. One study found no significant difference in serum potassium level or CK clearance between 0.9% normal saline versus lactated Ringer's solution [67]. While 0.9% normal saline may be given initially, multiple liters can lead to iatrogenic hyperchloremic metabolic acidosis, which can decrease urinary clearance of myoglobin [12].

Key Point. Management includes treatment of the underlying etiology and fluid rehydration, with a goal urine output of 300 mL/h.

As discussed, rhabdomyolysis is also associated with decreased urine pH [4,6]. Therefore, some experts have suggested adding bicarbonate (one ampule in 1 L of half normal saline or 2–3 ampules in 1 L of 5% dextrose) to IV fluids to facilitate renal excretion of myoglobin and reduce urine acidosis [6,12]. It is important to note that large doses of bicarbonate may worsen the degree of hypocalcemia, and caution is recommended if patients are already significantly hypocalcemic [3,4,11]. However, in the setting of hypocalcemia, administration of calcium chloride or gluconate should be avoided unless the patient develops hyperkalemic ECG changes, as calcium supplementation can worsen muscular injury and may lead to delayed-onset hypercalcemia [3,11]. Mannitol is an osmotic diuretic which was originally thought to promote increased renal blood flow, reduce renal cast formation, and act as a free-radical scavenger, administered as a 0.5 g/kg IV bolus of 20% mannitol, followed by a 0.1 g/kg/h infusion after restoration of intravascular volume [3,6,22,66,68,69].

There is no randomized controlled trial evidence to suggest additional benefit with sodium bicarbonate or mannitol over aggressive fluid resuscitation alone in reducing acute renal injury, need for dialysis, or death [3,4,13,51]. Mannitol may worsen renal perfusion and injury if

administered before restoration of intravascular volume. One study of patients with mild rhabdomyolysis (CK < 5000 IU/L) compared patients treated with bicarbonate and mannitol with those treated with saline alone and found no significant difference in renal outcomes [70]. Another study of trauma patients with rhabdomyolysis demonstrated no significant difference in outcomes with bicarbonate or mannitol up to a CK of 30,000 IU/L. [13] It is unclear whether this would be beneficial among patients with more severe rhabdomyolysis and CK levels above 30,000 IU/L. [13] Furosemide 40–120 mg per day has been previously advocated for forced diuresis [4]. However, similar to mannitol and bicarbonate, it does not demonstrate additional benefits in rhabdomyolysis beyond fluid resuscitation [12,51,66]. Loop diuretics may worsen urine acidosis, and there is no benefit in mortality, need for dialysis, or length of stay for furosemide in patients with rhabdomyolysis and renal injury [1-4,71]. Mannitol, sodium bicarbonate, and furosemide should not be routinely used for rhabdomyolysis based on the present literature.

While conservative therapy using the above strategies is preferred, renal replacement therapy (RRT), specifically continuous RRT (CRRT), should be considered in patients who are anuric with elevated creatinine or who experience life-threatening hyperkalemia, hypercalcemia, or hyperazotemia [22,58]. However, only 4% to 20% of patients with AKI caused by rhabdomyolysis typically require RRT [31,72,73]. CRRT is associated with more stable patient hemodynamics compared to intermittent RRT while removing myoglobin and other inflammatory molecules [74,75]. A Cochrane review states there is low quality evidence that CRRT may improve myoglobin clearance, as well as improve serum creatinine, blood urea nitrogen, and potassium levels [75]. However, it does not improve mortality [75]. Discussion of RRT should be made in conjunction with a nephrologist.

Key Point. Sodium bicarbonate, mannitol, and loop diuretics are not associated with improved outcomes. CRRT should be considered in anuric patients with elevated creatinine or those with life-threatening hyperkalemia, hypercalcemia, or hyperazotemia.

2.6. Disposition

Most patients with rhabdomyolysis will require admission for rehydration and evaluation for complications. However, exertional rhabdomyolysis is often a benign disease, with the majority of patients recovering without long-term renal injury or the need for RRT [42,43,76-80]. Patients with mild symptoms, clear etiology, normal vital signs, normal renal function and electrolytes, and ability to take oral fluids may be appropriate for discharge with follow up [42,43,76-80]. However, patients with uncertain etiology, laboratory abnormalities (including renal injury), those with prior episodes of rhabdomyolysis, and abnormal vital signs should be admitted for further treatment and evaluation [1-5,77]. While CK values in isolation are poorly predictive of the need for RRT [51,60,76-80], McMahon and colleagues derived and validated a risk stratification tool comprised of age, gender, underlying etiology, and initial laboratory values (i.e., calcium, CK, phosphate, and bicarbonate) (Table 2) [73]. Based on the study, patients at the lowest risk score (<5) had a 2.3% risk of death or need for RRT, while patients at the highest risk score (>10) had a 61.2% risk of death or need for RRT [73]. Knowledge of these risks may assist with determining whether patients should be admitted to the general medical floor or intensive care unit.

Several other rules have been produced to determine the risk of AKI with rhabdomyolysis [81,82]. However, these scores utilize lactate dehydrogenase, serum creatinine, and uric acid levels on multiple days, limiting their use in the ED. [81,82] Overall, there are limited to no high-quality data evaluating discharge for rhabdomyolysis, or the use of observation units. Further study is needed.

Key Point. Patients with uncertain etiology for rhabdomyolysis, laboratory abnormalities (including renal injury), those with prior episodes of rhabdomyolysis, and abnormal vital signs should be admitted. However, patients with a first episode of exertional rhabdomyolysis may be appropriate for discharge in the setting of mild symptoms, normal vital signs, normal renal function and electrolytes, and ability to take oral fluids.

Table 2
Risk prediction score for renal failure or mortality among patients with rhabdomyolysis [73].

Variable	Score
Age (years)	
>50 to ≤70	1.5
>70 to ≤80	2.5
>80	3
Female sex	1
Initial creatinine (mg/dL)	
1.4 to 2.2	1.5
>2.2	3
Initial calcium < 7.5 mg/dL	2
Initial CK > 40,000 IU/L	2
Origin not seizures, syncope, exercise, statins, or myositis	3
Initial phosphate (mg/L)	
4.0 to 5.4	1.5
>5.4	3
Initial bicarbonate < 19 mEq/L	2

CK, creatinine kinase.

3. Conclusions

Rhabdomyolysis is a medical condition caused by muscle breakdown leading to the release of a number of intracellular elements and protein molecules, including potassium, calcium, phosphate, uric acid, and creatinine kinase. Potential etiologies include trauma, exertion, extreme temperature changes, ischemia, infections, immobility, drugs, toxins, endocrine disorders, autoimmune reactions, and genetic conditions. History and examination findings can include myalgias, muscle weakness, or dark-colored urine, but often are non-specific. The diagnosis is determined by an elevated creatinine kinase, typically defined as greater than five times the upper-limit of normal. Treatment includes addressing the underlying etiology, as well as aggressive rehydration with a goal urine output of 300 mL/h. Bicarbonate, mannitol, and loop diuretics are not associated with improved outcomes. Renal replacement therapy should be determined on a case-by-case basis in consultation with a nephrologist. Emergency physicians should be knowledgeable regarding appropriate diagnosis and treatment options, as they are likely to care for such patients on a regular basis in the ED.

Conflicts of interest

None.

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