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Rhabdomyolysis: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document

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ABSTRACT

Rhabdomyolysis is a clinical condition characterized by destruction of skeletal muscle with release of intracellular contents into the bloodstream. Intracellular contents released include electrolytes, enzymes, and myoglobin, resulting in systemic complications. Muscle necrosis is the common factor for traumatic and non-traumatic rhabdomyolysis. The systemic impact of rhabdomyolysis ranges from asymptomatic elevations in bloodstream muscle enzymes to life-threatening acute kidney injury and electrolyte abnormalities. The purpose of this clinical consensus statement is to review the present-day diagnosis, management, and prognosis of patients who develop rhabdomyolysis.

INTRODUCTION

The American Association for the Surgery of Trauma (AAST) Critical Care Committee develops clinical consensus documents for critical care-related aspects of patient care. The goal of these documents is to provide practical answers to common clinical questions based on the best evidence available. They address focused topics for which the levels of evidence guiding care may not be strong and/or practice is controversial, and are based on expert consensus and review of the literature. This issue focuses on the diagnosis and management of rhabdomyolysis in the critically ill surgical/trauma patient.

METHODS

The topic for this document was chosen through discussion by the AAST Critical Care Committee. A subgroup was formed composed of the document's authors. The subgroup formulated the clinical questions to be addressed and assigned research and writing tasks. Authors were tasked with researching their clinical questions through literature review and writing their section. Literature review was performed by the individual authors pertaining to their clinical questions. Recommendations, references, and content were then reviewed by the subgroup and revised based on feedback to achieve consensus. The subsequent draft was distributed to the committee for review and comment prior to final editing by the first and last authors.

BACKGROUND

Rhabdomyolysis is a condition characterized by primary (mechanical) or secondary (metabolic) skeletal muscle injury, resulting in cell death and release of potentially toxic substances into circulation. Management often centers on prevention or treatment of the primary complication of the condition, acute kidney injury (AKI). Here we briefly review the causes, diagnosis, management, and outcomes of rhabdomyolysis.

In what patient populations should rhabdomyolysis be suspected?

Trauma patients

Recommendation

Rhabdomyolysis should be suspected in patients with a large burden of traumatic injury involving muscular tissue, especially patients with crush injuries involving the extremities or mangled extremities. Patients with vascular injuries or muscle ischemia with subsequent reperfusion are also at higher risk for rhabdomyolysis.

Discussion

Rhabdomyolysis is the result of skeletal muscle breakdown with release of potentially toxic substances such as electrolytes, myoglobin, and sarcoplasmic proteins into the bloodstream.[1] The pathophysiology underlying all cases of rhabdomyolysis is disruption of the myocyte cell membrane and leakage of cell contents into circulation.[2] This may result from direct myocyte injury related to trauma or from metabolic disturbances affecting supply of ATP within the myocyte.[3]

Traumatic injuries are a common cause of rhabdomyolysis. One study has shown some degree of biochemical evidence of rhabdomyolysis (abnormal creatine kinase (CK)) among 85% of critically injured patients admitted to a trauma intensive care unit setting, although only 10% developed renal failure and only 5% required renal replacement therapy (RRT).[4] Patients with multisystem trauma, crush injuries involving the extremities or torso, and those with compartment syndrome of one or more extremities are at highest risk.[5] Other independent risk factors for rhabdomyolysis among trauma patients include age older than 55 years, Injury Severity Score greater than 16, penetrating trauma with vascular injury, severe extremity injury, male sex, and body mass index greater than 30 kg/m^2.[4 6] Patients who fall with subsequent prolonged immobilization are also at higher risk for rhabdomyolysis, particularly if their limbs are compressed by their head or torso for a significant period of

time, leading to muscle hypoxia.[3] Conditions leading to skeletal muscle ischemia, such as direct compression or compartment syndrome, may lead to irreversible damage to the muscle; much of the injury may actually occur with reperfusion, in addition to injury sustained during the period of ischemia.[7] Trauma is a common cause of rhabdomyolysis, but less than 20% of all cases of rhabdomyolysis are thought to be related to direct injury; metabolic or medical causes of rhabdomyolysis are more common.[8]

Metabolic etiologies

Recommendation

Rhabdomyolysis should be suspected in any patient with a medical condition causing increased metabolic demands on myocytes in excess of the available supply of ATP. This may result from extreme exertional demands on skeletal muscle from exercise, exogenous agents such as drugs or toxins, genetic defects or myopathies affecting the muscle cell, and infections.

Discussion

Any process that impairs ATP production by skeletal muscle and any state where skeletal muscle energy requirements exceed the available ATP may lead to rhabdomyolysis.[3] With ATP depletion, active transport pumps are no longer able to maintain low levels of intracellular calcium; unregulated increases in intracellular calcium lead to activation of calcium-dependent enzymes with eventual breakdown of the muscle cell.[1] Exertional causes of rhabdomyolysis may include extreme and prolonged exercise or seizure activity such as status epilepticus.[9] Most commonly, drugs and toxins lead to rhabdomyolysis. Alcohol abuse or dependence may actually be the most common risk factor for rhabdomyolysis; ethanol has direct adverse effects on muscle tissue metabolism and cellular integrity including inhibition of active transport pumps.[3 8] Other illicit substances such as cocaine, heroin, and phencyclidine may also be implicated in cases of rhabdomyolysis. Lipid-lowering agents, especially statins, are a common cause of rhabdomyolysis, particularly in patients with concomitant renal or liver insufficiency.[10] Infections such as influenza, Epstein-Barr virus, *Streptococcus pyogenes*, or *Staphylococcus aureus* may rarely lead to rhabdomyolysis.[1] Genetic diseases including disorders of glycolysis or glycogenolysis, lipid metabolism defects, or mitochondrial disorders are rare causes of rhabdomyolysis.[1] Finally, rhabdomyolysis may be seen in patients with extreme alterations in body temperature due to conditions such as malignant hyperthermia, heat stroke, or neuroleptic malignant syndrome.[11] Metabolic etiology for rhabdomyolysis is very broad and a number of different risk factors may need to be considered in this population.

CLINICAL MANIFESTATIONS

What clinical findings are expected with rhabdomyolysis?

Recommendation

Rhabdomyolysis presentation may vary from asymptomatic to commonly implicated clinical features, including acute muscle weakness, pain/tenderness, and swelling (dolor, tumor) of the affected extremity or body region.[12] Darkened (tea-colored) urine may be an additional common finding. A low threshold of clinical suspicion in the proper laboratory and historical context is warranted to initiate appropriate therapy.

Discussion

Rhabdomyolysis is a clinical syndrome consequent to skeletal muscle cell death with release of intracellular contents (described in next section) into the circulation.[12] Resultant organ dysfunction may include renal (AKI), cardiac (arrhythmia), and coagulopathy. Despite this cluster of findings, there is no formally held definition for rhabdomyolysis and clinical presentations may vary greatly. Commonly implicated muscle groups are the extremities and the lower back. Superficial pressure ulceration or blistering may suggest the diagnosis, but is not a reliable finding. At the extremes of pathology, compartment syndromes of affected muscle groups lead to increased morbidity and potential need for decompression.[13]

What laboratory findings aid in the diagnosis of rhabdomyolysis?

Recommendation

The most commonly implicated variables include elevated serum concentrations of CK (>5× the upper limit of normal or >1000 IU/L), myoglobin, lactate dehydrogenase (LDH), potassium, creatinine, and aspartate aminotransferase (AST). Elevated urine myoglobin provides additional evidence. A low threshold of suspicion in the proper clinical context is warranted to initiate appropriate therapy. A strategy for disease monitoring with serial CK measurement should be additionally undertaken. Interval CK values should be followed until a peak concentration is identified (typically at 24–72 hours), discontinued once the CK is reliably downtrending.

Discussion

Traumatic or non-traumatic injury to the skeletal muscle cellular membrane leads to an influx of calcium into the cytoplasm, disrupting cellular homeostasis and leading to cell death. Injury may be exacerbated by the generation of reactive oxygen species after restoration of blood flood to the affected tissue (reperfusion injury). The resulting effect is the accumulation of CK, myoglobin, LDH, and potassium in the circulation.[2] In a recent systematic review, the laboratory definition of rhabdomyolysis varied to include an elevated CK level >5× the upper limit of normal or >1000 IU/L, with the CK-MM subtype being the most reflective of skeletal muscle injury.[1 2] CK values may become elevated within 12 hours of injury, peak at 24 to 72 hours, and return to normal in roughly 5 days, depending on the degree of injury and appropriate therapy.

Myoglobin becomes elevated in the circulation once intrinsic binding proteins are overwhelmed. Given a shorter half-life (1–3 hours) versus CK, myoglobin may elevate and resolve prior to CK depreciating its clinical utility. Myoglobin may also be evident in the urine and, although the sensitivity has been reported up to 100%, the specificity varies widely from 15% to 88%.[5] Although a causal relationship may exist between rhabdomyolysis and elevations in hepatic aminotransferases (AST, ALT: alanine transaminase), this is of unclear value as both enzymes exist within skeletal muscle and may become elevated as a result of primary muscle injury.[7 8 14 15]

MANAGEMENT

What is the optimal crystalloid type, rate of administration, and urine output goals to prevent AKI in rhabdomyolysis?

Recommendation

Either lactated Ringer's solution or saline (0.9% or 0.45%) is an acceptable fluid for resuscitation in rhabdomyolysis. A starting rate of 400 mL/hour can be initiated, with goal-directed therapy of urine output of 1 mL/kg/hour to 3 mL/kg/hour, and up to 300 cc/hour.

Discussion

Although early-volume resuscitation in rhabdomyolysis is well accepted as a mainstay of promoting renal tubule flow, diluting nephrotoxins such as myoglobin, and supplying adequate renal perfusion to prevent AKI, the best type of crystalloid for this purpose remains controversial.[1 16–18] The two most commonly cited fluids used for this resuscitation are lactated Ringer's solution and saline (0.9% or 0.45%). Saline is promoted due to its lack of potassium; in rhabdomyolysis, crush injury can lead to hyperkalemia and there is a theoretic concern for worsening this issue by using a potassium-containing fluid for resuscitation. Conversely, receiving large amounts of resuscitation with normal saline can lead to metabolic acidosis, which can be counterproductive if urine alkalinization is desired.[16] The only randomized controlled trial comparing these crystalloid fluid types evaluated patients with doxylamine-induced rhabdomyolysis.[19] Of note, in this study, urine pH was a targeted end goal, with a goal pH >6.5. In patients who received lactated Ringer's solution, urine and serum pH were significantly higher after 12 hours of aggressive resuscitation with significantly less need for bicarbonate administration to achieve goal urine pH, and there was no difference between groups in serum potassium level. However, there was also no difference in median time to serum CK less than 200 IU/L, which arguably is the most clinically relevant outcome in the study. There have been no other randomized controlled trials comparing lactated Ringer's solution and normal saline or 0.45% saline and therefore no clear recommendation as to which fluid type is better. It does appear that use of either type of fluid is safe in the treatment of rhabdomyolysis, so although this area certainly requires further study, at this time the type of fluid used for management of rhabdomyolysis may be at the discretion of the treating physician.

The rate of administration of intravenous fluids in rhabdomyolysis should be targeted to the patient as there is significant risk of volume overload should an excessive amount of fluid be given without goal-directed therapy. A starting rate of 400 cc/hour with a range of 200 cc/hour to 1000 cc/hour is considered reasonable but should be titrated to urine output, ensuring the patient is receiving adequate resuscitation without suffering from fluid creep.[1 19]

Urine output is the traditional method by which one can determine the adequacy of resuscitation in rhabdomyolysis. The most commonly cited urine output goals for intravenous fluid rehydration are 1 mL/kg/hour to 3 mL/kg/hour, and up to 300 mL/hour.[1–4 18 20–22] However, should the patient remain anuric despite escalating rates of intravenous fluid administration, the need for RRT may be necessary as ongoing aggressive fluid resuscitation without renal clearance could lead to significant and life-threatening volume overload.

Are diuretics and/or bicarbonate administration beneficial?

Recommendation

Clinical studies evaluating the efficacy of sodium bicarbonate and/or diuretic use (mannitol, loop diuretics) for prevention of rhabdomyolysis-induced AKI are limited by a lack of appropriate control groups, standardized definitions, retrospective design, and low statistical power. Given these significant limitations, the use of sodium bicarbonate or diuretics for prevention of AKI in rhabdomyolysis is not recommended.

Discussion

The precise mechanism of AKI in rhabdomyolysis is controversial and likely multifactorial. The two important factors in the development of myoglobin-induced renal toxicity are hypovolemia and aciduria.[23] Ferrihemate, which is a breakdown product of myoglobin, in the presence of a low pH can generate free radicals which can lead to direct renal cell injury. Furthermore, heme proteins can potentiate renal vasoconstriction, which may have been initiated by hypovolemia and can activate the cytokine cascade.[23–25] Pigmented casts, which are the hallmark of rhabdomyolysis-associated AKI, have been suggested to arise as a result of an interaction between the Tamm-Horsfall protein and myoglobin in an acidic environment. Other mechanisms that have been suggested propose that the precipitation of heme protein and its ability to generate free radicals at a low pH with resultant toxicity to the tubules is what may give way to cast formation.[23 24] Ultimately, AKI is the result of the combination of vasoconstriction, oxidant injury, and tubular obstruction, which leads to decreased glomerular filtration.

For the aforementioned reasons, it has been suggested that alkalinization of the urine may minimize renal injury in rhabdomyolysis and may ameliorate or prevent AKI. Furthermore, mannitol, an osmotic diuretic, is a potentially attractive therapeutic option in this setting, given its capacity for renal vasodilation, free radical scavenging, and potential for reduction of muscle compartment pressures.[1 26] There is no strong clinical evidence supporting the use of sodium bicarbonate administration and/or mannitol to prevent AKI in rhabdomyolysis.[26–28] Randomized controlled studies are lacking and the literature is composed mainly of retrospective studies or small case series. Many of these studies also lack a therapeutic endpoint such as measurement of urinary pH, and furthermore most of the studies couple mannitol use along with sodium bicarbonate.[18] One of the larger studies from Brown *et al*[4] reviewed 382 patients with rhabdomyolysis, composed of a subset of 1771 patients with CK >5000 U/L; 154 (40%) received bicarbonate and mannitol and 228 (60%) did not receive either bicarbonate or mannitol. There was no difference between groups in the rate of AKI or the need for RRT.[4] Similarly, Homsi *et al*,[29] in a study of 24 patients, retrospectively compared saline versus a combination of saline/mannitol/bicarbonate resuscitation for rhabdomyolysis (CK >500 IU/L) and found no difference in the incidence of renal failure between groups.[29] Nielsen *et al*[30] retrospectively evaluated normal saline with mannitol and bicarbonate versus normal saline alone in patients with traumatic rhabdomyolysis. They used a predefined protocol at their institution for patients with rhabdomyolysis with CK >10 000 U/L. Only 46 of 56 patients who would have qualified for the protocol had received it. When comparing these 46 with the 10 patients who did not receive the protocol, they recognized a significant decrease in the development of AKI in those patients receiving the protocol (26%) versus those who did not (70%).[30] The question as to which particular component of the protocol was beneficial and the impact of a standardized approach was not answered in this study. Furthermore this study also highlights the fact that the majority of the studies are fairly small and underpowered to demonstrate a clear benefit. A recent comprehensive review of the role of bicarbonate and mannitol in rhabdomyolysis demonstrates that aggressive early-volume therapy with normal saline should be the primary management and that bicarbonate and mannitol utilization should be discouraged.[26]

The clinical evidence supporting the use of loop diuretics in this setting is sparse and composed primarily of case reports.[31–34] As such, it cannot be interpreted with any confidence. Although loop diuretics have been shown to reduce metabolic demand and oxygen consumption by the proximal tubular cells, they have also been shown to worsen renal afferent arteriole

vasoconstriction, acidify urine, and promote aggregation of the Tamm-Horsfall protein within the tubular lumen. Taken together, the pathophysiologic consequences of loop diuretics may potentiate precipitation of myoglobin and worsen the distal tubular obstruction.[35 36] Additionally, hypokalemia due to loop diuretic use has been reported to result in hypokalemic myopathy and rhabdomyolysis.[37]

What electrolyte abnormalities should be expected and what are the optimal methods for management?

Recommendation

Hyperkalemia, hyperphosphatemia, and hypocalcemia are electrolyte abnormalities most commonly encountered when treating rhabdomyolysis. Correcting biochemical equilibrium and electrolytes during rhabdomyolysis should proceed meticulously to avoid complications from treatment. Hyperkalemia is the electrolyte abnormality that requires timely correction to reduce risk of cardiac arrhythmia.

Discussion

In rhabdomyolysis, electrolyte abnormalities occur as a result of cellular component release associated with induced AKI. Electrolyte abnormalities that occur due to rhabdomyolysis are hyperkalemia, hyperphosphatemia, hypocalcemia, and hypomagnesemia.

AKI in rhabdomyolysis is often associated with excessive potassium levels and correlates with the volume of muscle destruction. Baseline levels of potassium and all pertinent electrolytes should be evaluated when the possibility of rhabdomyolysis development is present. Hyperkalemia that occurs in rhabdomyolysis-induced AKI occurs early in the course of the disease process and should be monitored closely. Potassium levels should be serially evaluated. Patients with high potassium levels (>6 mmol/L) should have cardiac monitoring. ECG should be obtained and assessed for manifestations of severe hyperkalemia (QRS widening, small p waves, and severe arrhythmias). Hypocalcemia aggravates the electrical effects of hyperkalemia and should be aggressively treated with calcium chloride or calcium gluconate in this scenario. Elevated potassium levels should be treated with insulin and glucose infusions. Consider administration of a β-2 adrenergic agent such as albuterol via aerosol inhalation. Lastly, consider potassium removal via cation exchange resin or dialysis as indicated.[1 2 38 39]

Similar to hyperkalemia, hyperphosphatemia occurs as a result of phosphate release from damaged muscle cells. High levels of phosphate may be problematic because phosphate binds to calcium and this complex deposits in the soft tissues. Additionally, by inhibiting 1α-hydroxylase, hyperphosphatemia inhibits calcitriol formation and thus limits formation of the active form of vitamin D. Treatment of hyperphosphatemia should be done with caution since treatment involves administration of a calcium chelator which can increase precipitation of calcium phosphate in injured muscle. Early hyperphosphatemia typically decreases as phosphate is excreted in the urine.[1 2]

Hypocalcemia occurs early in rhabdomyolysis due to calcium entry into damaged cells and calcium phosphate deposition in necrotic muscle. Early hypocalcemia treatment in rhabdomyolysis should be avoided unless patients are symptomatic or severe hyperkalemia is present. Correction of hypocalcemia with calcium chloride or gluconate should be avoided since calcium deposition may occur in injured muscle. During the recovery phase, serum calcium levels return to normal and may rebound, causing hypercalcemia due to release of calcium from injured muscle and mild secondary hyperparathyroidism secondary to AKI.[1 2 40 41]

Hypermagnesemia seen with rhabdomyolysis is infrequent but when it occurs is typically in association with AKI and should be treated accordingly with hemodialysis.[1]

What is the role of RRT in rhabdomyolysis?

Recommendation

There is no role for RRT (either continuous (CRRT) or intermittent) in rhabdomyolysis to prevent AKI. The utilization of RRT in patients with rhabdomyolysis should be based on traditional indications for AKI and the degree of renal impairment.

In patients with rhabdomyolysis who develop AKI and need RRT, either CRRT or intermittent RRT should be used based on the degree of renal impairment and the clinical status of the patient. There are no recommendations regarding RRT modalities (filtration vs. diffusion), filter type (low vs. high cut-off membranes), or high-flow versus low-flow dialysis.

Discussion

Since AKI in rhabdomyolysis is associated with myoglobinuria, it has been proposed that extracorporeal removal of myoglobin may be an effective preventative strategy.[1 42] Despite case reports using plasmapheresis,[43] it has not been shown to have an effect on outcome or myoglobin clearance.[44] Furthermore, there is insufficient evidence to recommend RRT in the prevention of AKI in rhabdomyolysis.[38 45] Indeed, a Cochrane review evaluated CRRT for rhabdomyolysis. It sought to assess the efficacy of CRRT in myoglobin reversal, the influence of CRRT on mortality and kidney-related outcomes, and to evaluate the safety of CRRT for treatment in patients with rhabdomyolysis.[39 46–48] There was no significant difference in mortality compared with conventional therapy. The review concluded that overall the studies had poor quality and there was insufficient evidence to determine any benefits of CRRT over conventional therapy for rhabdomyolysis and prevention of AKI in rhabdomyolysis.

There have been several studies investigating myoglobin clearance using different dialysis modalities, filters, and flow types. The RRT techniques in these studies were initiated based on traditional indications for AKI and sought to determine if any of these different modalities, filter, and flow types facilitate myoglobin clearance and hence affect kidney-related outcomes. Since myoglobin has a molecular weight of 17 KDa and is thought to be poorly cleared by diffusion (dialysis), investigators have studied whether the technique of RRT (continuous vs. intermittent), hemodiafiltration versus hemofiltration, use of special high cut-off membrane filters (which enhance clearance of larger molecules), as well as high-flow versus low-flow dialysis improve overall or kidney-related outcomes.[49–53] The overall studies are small in number and seem to lack sufficient evidence to make any recommendations.

The utilization of RRT in patients with rhabdomyolysis should be based on traditional indications for AKI and the degree of renal impairment, such as severe acid/base disturbances, electrolyte abnormalities, and hypervolemia, all of which are refractory to medical management.

OUTCOMES

What complications should be suspected by clinicians treating rhabdomyolysis?

Recommendation

Clinicians should monitor for a variety of complications, ranging from an asymptomatic elevation of muscle protein to

an accumulation of electrolyte imbalances, edema, and toxic cellular components. Morbidity can present early or late, including hyperkalemia, hepatic dysfunction, cardiac dysfunction, AKI, acute renal failure (ARF), disseminated intravascular coagulation (DIC), and compartment syndrome. AKI is the most common systemic complication of rhabdomyolysis and is responsible for most of the morbidity and mortality associated with rhabdomyolysis.

Discussion

In rhabdomyolysis, hyperkalemia is the most significant electrolyte abnormality.[54] Hepatic dysfunction occurs in approximately 25% of patients with rhabdomyolysis. Proteases released from injured muscle may be implicated in hepatic inflammation. Cardiac symptoms may be secondary to electrolyte abnormalities, such as severe hyperkalemia, and range from dysrhythmia to cardiac arrest.[2]

The overall mortality among inpatients with CK >5000 IU/L is approximately 14%.[22] ARF develops in up to 15% of patients. Among those requiring RRT, mortality may be as high as 59%.[54] Additionally, the release of intracellular products may activate the clotting cascade, leading to DIC in patients with rhabdomyolysis.[22 54] This presentation is often subclinical with prolonged coagulation studies, thrombocytopenia, and elevated fibrin degradation studies without significant bleeding or thrombosis.[54] Compartment syndrome may be an early or late complication, resulting from direct muscle injury or vigorous muscle activity. This complication occurs primarily due to limited muscle expansion from enveloping tight fascia. A delay of more than 6 hours in diagnosing this complication can lead to irreversible muscle damage or death.[53]

Can prediction scoring be used in rhabdomyolysis?

Recommendation

The risk of AKI, RRT, and/or in-hospital mortality in patients with rhabdomyolysis can be estimated using admission demographic, clinical, and laboratory variables. Risk prediction scores may not directly influence treatment; however, they may be useful in estimating prognosis and setting expectations.

As no single laboratory value is sufficient to predict the course of rhabdomyolysis, a combined index of metrics, the McMahon Score (table 1), may be calculated at admission for prognostication.[3] A score greater than or equal to 6 is predictive of a need for high-volume fluid resuscitation, RRT, and death.

Table 1 McMahon Score

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

Discussion

Rhabdomyolysis is a syndrome characterized by deposition of muscle protein that can be life-threatening, and identification of severity biomarkers is key. CK is usually taken as a reference to estimate prognosis; however, this is not the most effective parameter.[22] McMahon *et al*[55] performed a retrospective cohort study to develop a risk prediction tool to identify patients at greatest risk of RRT or in-hospital mortality. In total, these outcomes occurred in 19.0% of patients with rhabdomyolysis.[55] The independent predictors identified were age, female sex, cause of rhabdomyolysis, and values of initial creatinine, creatine phosphokinase, phosphate, calcium, and bicarbonate. In the validation cohort, among patients with the lowest risk score (<5), 2.3% died or needed RRT. Among patients with the highest risk score (>10), 61.2% died or needed RRT.[54] Rodríguez *et al*[56] conducted a retrospective observational cohort study to assess the risk factors for AKI and to develop a risk score for early prediction. The variables of peak CK, hypoalbuminemia, metabolic acidosis, and decreased prothrombin time were independently associated with AKI. A risk score for AKI was calculated for each patient, with an OR of 1.72 (95% CI 1.45 to 2.04).[56]

Several other retrospective studies brought forth other prediction variables for AKI, ARF, and need for RRT. Baeza-Trinidad *et al*[57] found initial creatinine levels associated with progression to AKI and mortality at 30 days. The cut-off point of creatinine of 1.15 mg/dL had the best ratio of sensitivity (74.6%) and specificity (67.4%) to predict mortality.[57] Chen *et al*[58] looked at predictive factors for ARF including dark urine, initial and peak serum myoglobin level, rhabdomyolysis caused by body temperature change, and elevated serum potassium. Risk factors for RRT initiation were peak BUN (Blood Urea Nitrogen)/creatinine levels and CK level on the third day as rhabdomyolysis developed. The initial serum myoglobin threshold associated with development of ARF is 600 ng/mL.[58] In ambiguous cases, clinical suspicion of rhabdomyolysis is confirmed by a positive urine or serum test for myoglobin. There is a loose correlation between CK levels and the development of ARF, with levels higher than 16 000 IU/L more likely to be associated with renal failure.[22]

The McMahon Score is a prospectively validated risk prediction tool to identify patients at high risk of RRT or in-hospital mortality (table 1). When calculated at admission from demographic and blood chemistry data, a score ≥6 is 86% sensitive and 68% specific for patients who will require RRT. In this setting, the authors recommend the initiation of renal protective therapy with a target urine output of 1 mL/kg/hour to 3 mL/kg/hour, and up to 300 cc/hour.[1–4 18 20–22]

CONCLUSION

Rhabdomyolysis is a relatively uncommon but important condition seen in critically ill and injured patients. Surgical critical care providers should be familiar with the less frequently encountered metabolic etiologies of rhabdomyolysis, in addition to the well-known traumatic causes. The diagnosis is made with a combination of clinical and laboratory findings and should lead to prompt intervention to halt any processes causing muscle damage and to prevent or treat known complications of the disease. A consensus summary for the diagnosis and management of rhabdomyolysis is provided in (table 2). Although traditional therapies such as

Table 2 Rhabdomyolysis consensus summary

Problem	Recommendations/findings
Populations at risk	► Large burden of injury involving muscle. ► Vascular injury or muscle ischemia. ► Extreme exertional demands/toxins.
Clinical findings	► May be asymptomatic. ► Acute muscle weakness. ► Pain/tender/swelling involved extremity.
Laboratory findings	► CK >5× upper limit of normal or >1000 IU/L. ► Elevated myoglobin, LDH, K+, Cr, and AST.
Fluid management	► LR or NaCl (0.9 or 0.45%) initiated at 400 cc/hour.
Urine output goals	► 1–3 cc/kg/hour. ► Up to 300 cc/hour.
Diuretic/bicarbonate therapy	► Diuretics not recommended. ► Bicarbonate not recommended.
Electrolyte abnormalities	► Elevated K+ and phosphate. ► Decreased calcium.
Renal replacement therapy	► No role for RRT in AKI prevention. ► Rhabdo with AKI: CRRT or intermittent RRT. ► No recommendation on RRT modalities.
Complications of rhabdomyolysis	► AKI. ► DIC. ► Compartment syndrome.
Predictors of AKI development	► Based on demographic and clinical laboratory variables. ► McMahon Score for RRT need.

AKI, acute kidney injury; AST, aspartate aminotransferase; CK, creatine kinase; Cr, creatinine; CRRT, continuous renal replacement therapy; DIC, disseminated intravascular coagulation; K+, potassium; LDH, lactate dehydrogenase; LR, lactated Ringer's solution; RRT, renal replacement therapy.

urine alkalinization and diuresis are often employed in an effort to prevent rhabdomyolysis-associated AKI, evidence-based treatments with outcome benefits are lacking. There is a critical need for quality research.

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REFERENCES

1 Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med* 2009;361:62–72.
2 Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. *Crit Care* 2016;20:135.
3 Allison RC, Bedsole DL. The other medical causes of rhabdomyolysis. *Am J Med Sci* 2003;326:79–88.
4 Brown CVR, Rhee P, Chan L, Evans K, Demetriades D, Velmahos GC. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? *J Trauma* 2004;56:1191–6.
5 Oda J, Tanaka H, Yoshioka T, Iwai A, Yamamura H, Ishikawa K, Matsuoka T, Kuwagata Y, Hiraide A, Shimazu T, *et al*. Analysis of 372 patients with crush syndrome caused by the Hanshin-Awaji earthquake. *J Trauma* 1997;42:470–6.
6 Brown CVR, Rhee P, Evans K, Demetriades D, Velmahos G, Velhamos G. Rhabdomyolysis after penetrating trauma. *Am Surg* 2004;70:890–2.
7 Odeh M. The role of reperfusion-induced injury in the pathogenesis of the crush syndrome. *N Engl J Med* 1991;324:1417–22.
8 Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine* 1982;61:141–52.
9 Sinert R, Kohl L, Rainone T, Scalea T. Exercise-Induced rhabdomyolysis. *Ann Emerg Med* 1994;23:1301–6.
10 Hodel C. Myopathy and rhabdomyolysis with lipid-lowering drugs. *Toxicol Lett* 2002;128:159–68.
11 Guzé BH, Baxter LR. Neuroleptic malignant syndrome. *N Engl J Med Overseas Ed* 1985;313:163–6.
12 Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. *J Neurol* 2020;267:877–82.
13 Cabral BMI, Edding SN, Portocarrero JP, Lerma EV. Rhabdomyolysis. *Dis Mon* 2020;66:101015.
14 Lim AK. Abnormal liver function tests associated with severe rhabdomyolysis. *World J Gastroenterol* 2020;26:1020–8.
15 Lim AKH, Arumugananthan C, Lau Hing Yim C, Jellie LJ, Wong EWW, Junckerstorff RK. A cross-sectional study of the relationship between serum creatine kinase and liver biochemistry in patients with rhabdomyolysis. *J Clin Med* 2019;9:81.
16 Zimmerman JL, Shen MC. Rhabdomyolysis. *Chest* 2013;144:1058–65.
17 Shapiro ML, Baldea A, Luchette FA. Rhabdomyolysis in the intensive care unit. *J Intensive Care Med* 2012;27:335–42.
18 Scharman EJ, Troutman WG. Prevention of kidney injury following rhabdomyolysis: a systematic review. *Ann Pharmacother* 2013;47:90–105.
19 Cho YS, Lim H, Kim SH. Comparison of lactated Ringer's solution and 0.9% saline in the treatment of rhabdomyolysis induced by doxylamine intoxication. *Emerg Med J* 2007;24:276–80.
20 Simpson JP, Taylor A, Sudhan N, Menon DK, Lavinio A. Rhabdomyolysis and acute kidney injury: creatine kinase as a prognostic marker and validation of the McMahon score in a 10-year cohort: a retrospective observational evaluation. *Eur J Anaesthesiol* 2016;33:906–12.
21 Long B, Koyfman A, Gottlieb M. An evidence-based narrative review of the emergency department evaluation and management of rhabdomyolysis. *Am J Emerg Med* 2019;37:518–23.
22 Sauret JM, Marinides G, Wang GK. Rhabdomyolysis. *Am Fam Physician* 2002;65:907–12.
23 Guglielminotti J, Guidet B. Acute renal failure in rhabdomyolysis. *Minerva Anestesiol* 1999;65:250–5.
24 Zager RA. Studies of mechanisms and protective maneuvers in myoglobinuric acute renal injury. *Lab Invest* 1989;60:619–29.
25 Huerta-Alardín AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis -- an overview for clinicians. *Crit Care* 2005;9:158–69.
26 Somagutta MR, Pagad S, Sridharan S, Nanthakumaran S, Arnold AA, May V, Malik BH. Role of Bicarbonates and mannitol in rhabdomyolysis: a comprehensive review. *Cureus* 2020;12:e9742.
27 Zager RA, Foerder C, Bredl C. The influence of mannitol on myoglobinuric acute renal failure: functional, biochemical, and morphological assessments. *J Am Soc Nephrol* 1991;2:848–55.
28 Zager RA. Combined mannitol and deferoxamine therapy for myohemoglobinuric renal injury and oxidant tubular stress. mechanistic and therapeutic implications. *J Clin Invest* 1992;90:711–9.
29 Homsi E, Barreiro MF, Orlando JM, Higa EM. Prophylaxis of acute renal failure in patients with rhabdomyolysis. *Ren Fail* 1997;19:283–8.
30 Nielsen JS, Sally M, Mullins RJ, Slater M, Groat T, Gao X, de la Cruz JS, Ellis MKM, Schreiber M, Malinoski DJ. Bicarbonate and mannitol treatment for traumatic rhabdomyolysis revisited. *Am J Surg* 2017;213:73–9.
31 Eneas JF, Schoenfeld PY, Humphreys MH. The effect of infusion of mannitol-sodium bicarbonate on the clinical course of myoglobinuria. *Arch Intern Med* 1979;139:801–5.
32 Ron D, Taitelman U, Michaelson M, Bar-Joseph G, Bursztein S, Better OS. Prevention of acute renal failure in traumatic rhabdomyolysis. *Arch Intern Med* 1984;144:277–80.
33 Nadjafi I, Atef MR, Broumand B, Rastegar A. Suggested guidelines for treatment of acute renal failure in earthquake victims. *Ren Fail* 1997;19:655–64.
34 Knottenbelt JD. Traumatic rhabdomyolysis from severe beating--experience of volume diuresis in 200 patients. *J Trauma* 1994;37:214–9.
35 Kellum JA, Lameire N, . KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013;17:204.

36 Sanders PW, Booker BB. Pathobiology of cast nephropathy from human Bence Jones proteins. *J Clin Invest* 1992;89:630–9.
37 Shintani S, Shiigai T, Tsukagoshi H. Marked hypokalemic rhabdomyolysis with myoglobinuria due to diuretic treatment. *Eur Neurol* 1991;31:396–8.
38 Petejova N, Martinek A. Acute kidney injury due to rhabdomyolysis and renal replacement therapy: a critical review. *Crit Care* 2014;18:224.
39 Zeng X, Zhang L, Wu T, Fu P. Continuous renal replacement therapy (CRRT) for rhabdomyolysis. *Cochrane Database Syst Rev* 2014;6C:D008566.
40 Llach F, Felsenfeld AJ, Haussler MR. The pathophysiology of altered calcium metabolism in rhabdomyolysis-induced acute renal failure. interactions of parathyroid hormone, 25-hydroxycholecalciferol, and 1,25-dihydroxycholecalciferol. *N Engl J Med* 1981;305:117.
41 Akmal M, Bishop JE, Telfer N, Norman AW, Massry SG. Hypocalcemia and hypercalcemia in patients with rhabdomyolysis with and without acute renal failure. *J Clin Endocrinol Metab* 1986;63:137–42.
42 Ronco C. Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance. *Crit Care* 2005;9:141–2.
43 Swaroop R, Zabaneh R, Parimoo N. Plasmapheresis in a patient with rhabdomyolysis: a case report. *Cases J* 2009;2:8138.
44 Szpirt WM. Plasmapheresis is not justified in treatment of rhabdomyolysis and acute renal failure. *J Cardiovasc Surg* 1997;38:557.
45 Michelsen J, Cordtz J, Liboriussen L, Behzadi MT, Ibsen M, Damholt MB, Møller MH, Wiis J. Prevention of rhabdomyolysis-induced acute kidney injury - A DASAIM/DSIT clinical practice guideline. *Acta Anaesthesiol Scand* 2019;63:576–86.
46 Dong W. The treatment effect of continuous venovenous hemofiltration on crush syndrome. *Lin Chuang Yi Xue [Clin Med]* 2005;25:14–16.
47 Wang Z, Liu J. The efficacy of CAVHD for crush syndrome. *Hei Long Jiang Yi Yao Ke Xue [Heilongjiang Med Pharm]* 2008;31.
48 Zeng L, Mi X, Zhang J, Li C. The efficacy of CVVH for acute kidney injury induced by rhabdomyolysis. *Si Chuan Yi Xue [Sichuan Med J]* 2008;29:307–8.
49 Wakabayashi Y, Kikuno T, Ohwada T, Kikawada R. Rapid fall in blood myoglobin in massive rhabdomyolysis and acute renal failure. *Intensive Care Med* 1994;20:109–12.
50 Peltonen S, Ahlström A, Kylävainio V, Honkanen E, Pettilä V. The effect of combining intermittent hemodiafiltration with forced alkaline diuresis on plasma myoglobin in rhabdomyolysis. *Acta Anaesthesiol Scand* 2007;51:553–8.
51 Mikkelsen TS, Toft P. Prognostic value, kinetics and effect of CVVHDF on serum of the myoglobin and creatine kinase in critically ill patients with rhabdomyolysis. *Acta Anaesthesiol Scand* 2005;49:859–64.
52 Heyne N, Guthoff M, Krieger J, Haap M, Häring H-U. High cut-off renal replacement therapy for removal of myoglobin in severe rhabdomyolysis and acute kidney injury: a case series. *Nephron Clin Pract* 2012;121:c159–64.
53 Amyot SL, Leblanc M, Thibeault Y, Geadah D, Cardinal J. Myoglobin clearance and removal during continuous venovenous hemofiltration. *Intensive Care Med* 1999;25:1169–72.
54 Cote DR, Fuentes E, Elsayes AH, Ross JJ, Quraishi SA. A "crush" course on rhabdomyolysis: risk stratification and clinical management update for the perioperative clinician. *J Anesth* 2020;34:585–98.
55 McMahon GM, Zeng X, Waikar SS. A risk prediction score for kidney failure or mortality in rhabdomyolysis. *JAMA Intern Med* 2013;173:1821–8.
56 Rodríguez E, Soler MJ, Rap O, Barrios C, Orfila MA, Pascual J. Risk factors for acute kidney injury in severe rhabdomyolysis. *PLoS One* 2013;8:e82992.
57 Baeza-Trinidad R, Brea-Hernando A, Morera-Rodriguez S, Brito-Diaz Y, Sanchez-Hernandez S, El Bikri L, Ramalle-Gomara E, Garcia-Alvarez JL. Creatinine as predictor value of mortality and acute kidney injury in rhabdomyolysis. *Intern Med J* 2015;45:1173–8.
58 Chen C-Y, Lin Y-R, Zhao L-L, Yang W-C, Chang Y-J, Wu H-P. Clinical factors in predicting acute renal failure caused by rhabdomyolysis in the ED. *Am J Emerg Med* 2013;31:1062–6.