Rhabdomyolysis

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Rhabdomyolysis is characterized by skeletal muscle disintegration and the release of myoglobin and other intercellular proteins and electrolytes into the circulation. Typically, creatine kinase (CK) levels are markedly elevated and muscle pain and myoglobinuria may occur. The condition ranges from asymptomatic to life-threatening, with associated hyperkalaemia and acute kidney injury (AKI). Bywaters and Beall made the first association between AKI and crush injury during the London Blitz. They described four air-raid casualties with oliguria and pigmented casts after crush injury. All four patients developed AKI and died in about a week.

Key points

- Rhabdomyolysis is characterized by breakdown of skeletal muscle with the release of myoglobin and other intercellular proteins and electrolytes into the circulation.
- Creatine kinase concentration is the most useful indicator of muscle damage.
- Hyperkalaemia can be life-threatening and needs prompt management.
- Acute kidney injury is common.
- Fluid resuscitation is the mainstay of management.

Causes

Rhabdomyolysis can be traumatic or non-traumatic (Table 1). In one review of 26 intensive care patients, the cause was ischaemic by vascular obstruction (50%), crush injury by trauma (23%), sepsis (11.5%), heat stroke/hyperthermia (11.5%), and hyponatraemia in a single patient. Alcohol is commonly associated with rhabdomyolysis. Coma, whether from alcohol or other causes, can lead to prolonged muscle compression and ischaemia. Alcohol can also damage the sarcolemma directly and can cause myopathy, leading to non-traumatic rhabdomyolysis. In addition to causing rhabdomyolysis in its own right, chronic abuse renders the muscle vulnerable to further damage.

Pathophysiology

Rhabdomyolysis involves either direct sarcolemmic injury (usually trauma) or depletion of ATP within the myocyte. ATP stores maintain the ionic gradients across the cell membrane including the calcium ATPase pumps. Depletion of ATP impairs the function of these pumps and results in increased sarcoplasmic calcium levels leading to persistent contraction of the myofibril.

Metabolic derangements

After myocyte injury, intracellular contents are released into the circulation. Hyperkalaemia, hyperuricaemia, and hyperphosphataemia can all develop rapidly. High levels of phosphate withdraw from the USA in 2001, as the rate of rhabdomyolysis was 16–80 times as high as for any other statin. Fortunately, fatal rhabdomyolysis among statin users is rare, with reporting rates lower than one death per million prescriptions.

Anaesthesia obscures the pain and paresthesia of prolonged muscle compression that disturbs the conscious patient. The combination of surgery and anaesthesia can expose patients to muscle injury and rhabdomyolysis. Risk factors include prolonged immobility, use of tourniquets and non-invasive arterial pressure cuffs, and poor perioperative positioning. Compression of discrete muscle groups may occur in the lower limbs in the lithotomy position or on pressure points during pronation. Particular care to prevent localized pressure effects must be taken in these at-risk patients.

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bind to calcium, and calcium–phosphate deposition can occur in soft tissue. In addition, calcium is lost from the serum by entering damaged muscle cells with resultant hypocalcaemia. Ischaemic muscle is forced to utilize anaerobic metabolism via the conversion of pyruvate to lactate and a metabolic acidosis may occur. The combination of hyperkalemia, hyperuricaemia, and acidosis is particularly dangerous. Hyperuricaemia is caused by the metabolism of purines from disintegrated cell nuclei.

During the recovery phase of rhabdomyolysis, about one-third of patients develop hypercalcaemia. This may occur due to the release of vitamin D stores from injured muscle, providing substrate for the production of excess 1,25-dihydroxyvitamin D₃. Hypercalcaemia may be further exacerbated if excess calcium is administered during the acute hypocalcaemic phase.

Myoglobin is a dark red haem-containing protein that stores and transports oxygen in muscle. Only small levels of myoglobin are normally present in plasma. At normal levels, this small amount of myoglobin is bound to plasma proteins and very little crosses through the glomerulus. Myoglobin has a small molecular weight and is easily filtered. When this transport mechanism is overwhelmed, the renal threshold for free myoglobin is exceeded and myoglobin appears in the urine.

### AKI and rhabdomyolysis

During intensive care, the reported incidence of AKI after rhabdomyolysis may be as high as 65% and occurs as a result of multiple mechanisms including tubular obstruction, direct and ischaemic tubular injury, and intrarenal vasoconstriction. Within the renal tubules, myoglobin interacts with the protein Tamm–Horsfall to form brown granular casts and this results in tubular obstruction. This process is favoured when the urine is acidic and myoglobin may have no nephrotoxic effect when the urine is alkaline. Tubular obstruction may be compounded by deposition of urate as a result of hyperuricaemia. The haem group from myoglobin has been implicated in lipid peroxidation, with accompanying cytotoxic effects. The scavenging effect of myoglobin in the renal microcirculation results in a deficit of the vasodilator nitric oxide and renal vasoconstriction further compounding kidney injury. Renal blood flow is further reduced by hypovolaemia, activation of the renin–angiotensin system, and additional vascular mediators.

In a 44 month retrospective study of 135 consecutive patients with rhabdomyolysis, RIFLE criteria (Risk, Injury, Failure, Loss, End-stage) were used to stratify the severity of AKI. At admission, 44% had no AKI, 15% had risk, 24% had injury, and 17% had failure. These categories were associated with increasing magnitude of volume depletion, potassium, phosphate, urea, and the anion gap. They also predicted differences in length of stay, dialysis, discharge creatinine, and the rate of normalization of the admission creatinine.

### Clinical manifestation and investigations

A high level of suspicion for rhabdomyolysis is required in patients suffering trauma, crush injury, or prolonged immobilization. Where a specific muscle group is affected, a history of weakness, myalgia, and swelling in the affected limbs may be obtained. Severe pain may limit passive limb movement and there may be a reduction in the range of active movement. In compartment syndrome or crush injury, the muscles may be tense and swollen, leading to nerve injury with sensory loss. In diffuse muscle injury such as occurs with drugs, there may be a general malaise with diffuse myalgia and a non-specific deterioration. Rarely, patients may volunteer that their urine has changed to a red or brown colour. Commonly offending drugs such as statins, alcohol, heroin, and cocaine should be identified and withdrawn. Clinical observations may initially be normal or be normalized after fluid resuscitation only to deteriorate hours later as the condition progresses. Regular observations including hourly urine output are required to detect any deterioration promptly.

Rhabdomyolysis is typically diagnosed when the CK is $>5000$ units litre⁻¹. This value represents five times its normal upper limit. Myoglobin levels peak before increases in CK; however, myoglobin is metabolized rapidly at sites outside of the kidney. This makes CK a more reliable marker of rhabdomyolysis.

CK is predominantly of the skeletal muscle (MM) rather than the myocardial (MB) fraction. An increase in CK-MB represents the small amount found in skeletal muscle rather than cardiac injury. CK levels typically peak between 24 and 72 h after the onset of rhabdomyolysis. If CK continues to increase beyond this period, an undiagnosed compartment syndrome should be considered.

Serum and urine myoglobin can be measured directly but is not offered by all laboratories. Myoglobin is detectable in urine when the serum concentration exceeds the renal threshold of 0.5–1.5 mg dl⁻¹ and is directly visible as reddish-brown urine when concentration exceeds 100 mg dl⁻¹. As the increase in serum myoglobin precedes that of CK, and the metabolism of myoglobin is rapid, myoglobin levels may have become undetectable by the time urine levels are tested. In addition, the intrinsic property of the assay used to detect myoglobinuria is insensitive and may also reduce the frequency that myoglobinuria is detected.
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does not exclude rhabdomyolysis. In a study of 475 patients with rhabdomyolysis diagnosed by CK levels, myoglobinuria was only detected in 19%.

Urinary dipstick for blood is positive in the presence of myoglobin and has a sensitivity of 81% for the detection of rhabdomyolysis and is far more frequently present than a positive assay for myoglobin.14 A false positive will occur if urinary red cells are present as this impairs the reliability, especially in the setting of trauma. Urine dipstick is a rapid bedside test that can be used in a serial manner to assess for resolution of myoglobinuria, providing a useful endpoint for fluid resuscitation.

A metabolic acidosis with a high anion gap is commonly reported in rhabdomyolysis with associated AKI.16 Arterial blood gas analysis allows monitoring of trends in pH and serum lactate that can guide fluid resuscitation. In addition, pH, base excess, and potassium levels can be used to manage decisions regarding renal replacement therapy. Clotting studies should be taken to exclude disseminated intravascular coagulation that may occur at the more severe spectrum of rhabdomyolysis.

A list of common investigations required in those with suspected rhabdomyolysis is listed in Table 2.

Management

Early fluid resuscitation is the most important measure in the prevention of AKI. Large volume depletion occurs due to sequestration of water by injured muscle. Bladder catheterization is required to monitor urine output accurately and invasive monitoring such as arterial and central venous pressure monitoring should be considered to guide fluid resuscitation. Consideration of more advanced flow monitoring should be made on the decision of the individual units preference and local availability. Most studies target urine outputs of 3 ml kg⁻¹ h⁻¹ or >300 ml h⁻¹. Normal saline, compound sodium lactate (Hartmanns), and sodium bicarbonate have all been used in the literature as resuscitation fluids and have comparative merits and disadvantages. Compound sodium lactate may aid in urinary alkalization but should probably be avoided as it contains potassium. Normal saline is devoid of potassium and is more appropriate, but it may contribute to hyperchloreaemic acidosis. Volume resuscitation with polyuria should be continued until myoglobinuria is cleared as supported by a negative urinary dipstick for blood.

Alkalization of the urine by administration of sodium bicarbonate has theoretical advantages. This includes the reduced precipitation of Tamm–Horsfall protein complexes in the alkaline urinary environment. The disadvantage of alkalization is a reduction in ionized calcium that may further exacerbate the hypocalcaemia induced by phosphate–calcium precipitation. Sodium bicarbonate may be administered as boluses of 50–100 mmol or as 1.26% to aid in volume resuscitation. An advantage of the administration of 1.26% sodium bicarbonate is the avoidance of the hyperchloreaemic acidosis associated with large volumes of sodium chloride infusion. A target urinary pH of >6.5 should be achieved. Evidence for the use of sodium bicarbonate as a therapy to prevent AKI in rhabdomyolysis is lacking. A recent systematic review found no level 1–3 evidence to support its use.17

Mannitol also has theoretical benefits: it flushes nephrotoxic agents through the tubules, extracts fluid that has accumulated in injured muscle, and acts as a free radical scavenger. Mannitol may exacerbate hypovolaemia and therefore use should be reserved for when urine output remains low despite normovolaemia. Plasma osmolality and osmolar gap should be monitored and mannitol should be discontinued if there is no improvement in urine output or if the osmolar gap increases above 55 mOsm kg⁻¹.18 Other diuretics are not appropriate in this setting. Again there was no level 1–3 evidence to support the use of mannitol in the prevention of AKI.17

Of all the electrolyte abnormalities in rhabdomyolysis hyperkalaemia is the most life-threatening and should be monitored and treated promptly. Hyperkalaemic ECG changes should be treated with calcium gluconate 10 ml of 10%. Patients with hyperkalaemia >6.5 mmol⁻¹ should be given insulin 10 IU in 50 ml of 50% dextrose over 15 min and nebulized salbutamol 10 mg.19 Early hypocalcaemia should not be treated unless the patient becomes symptomatic or in the treatment of hyperkalaemia as normocalcaemia usually occurs spontaneously. Renal replacement therapy should be reserved for the management of hyperkalaemia, acidosis, or volume overload.

The European Renal Best Practice and Renal Disaster Relief Task Force of the International Society has produced recommendations for the management of crush victims in mass disasters.7 As the evidence base on this topic is sparse, they are based on retrospective analyses, case reports, position statements, and expert judgement or opinion, all of which represent a low grade of evidence. It describes the basic life-saving interventions in the disaster field such as early fluid resuscitation, extrication, and the medical and logistical recommendations that apply to major disasters.

Where compartment syndrome is suspected, initial management should focus on prompt diagnosis and relief of compartmental pressures. External pressure from dressings, casts, or rubble at trauma scenes must be removed. Oxygen should be administered and analgesia offered as pain often appears out of proportion to the injury sustained. Hypotension should be avoided as it further reduces limb perfusion. Urgent fasciotomy is commonly the definitive therapy and should be performed early. Delays in performing fasciotomy increase

Table 2 Investigations in rhabdomyolysis

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<thead>
<tr>
<th>Investigation</th>
<th>Possible findings</th>
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<tbody>
<tr>
<td>Creatine kinase</td>
<td>&gt;5000 units litre⁻¹</td>
</tr>
<tr>
<td>Serum and urine myoglobin</td>
<td>Present</td>
</tr>
<tr>
<td>Urinary dipstick + pH</td>
<td>Positive for blood</td>
</tr>
<tr>
<td>Urea and creatinine</td>
<td>Raised</td>
</tr>
<tr>
<td>Potassium</td>
<td>Raised</td>
</tr>
<tr>
<td>Calcium</td>
<td>Low</td>
</tr>
<tr>
<td>Phosphate, uric acid</td>
<td>Raised</td>
</tr>
<tr>
<td>Coagulation studies</td>
<td>Prolonged in severe cases</td>
</tr>
<tr>
<td>Blood gas</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Calculation of anion gap</td>
<td>Raised</td>
</tr>
<tr>
<td>ECG</td>
<td>Changes of hyperkalaemia</td>
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morbidity, including the need for amputation. After fasciotomy, patients should be closely monitored with serial CK levels and hourly urine output to detect impending rhabdomyolysis and AKI. High-risk patients with multiple injuries should be cared for in a critical care environment. Medical and surgical management of patients with established rhabdomyolysis should occur simultaneously.

The intensive care mortality from rhabdomyolysis has been reported as 22% without AKI and 59% with AKI; however, the majority of survivors recover good renal function.

**Declaration of interest**

None declared.

**References**


Please see multiple choice questions 13–16.