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REVIEW

Rhabdomyolysis: a review of the literature

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ABSTRACT

Rhabdomyolysis is a potentially life-threatening syndrome that can develop from a variety of causes; the classic findings of muscular aches, weakness and tea-coloured urine are non-specific and may not always be present. The diagnosis therefore rests upon the presence of a high level of suspicion of any abnormal laboratory values in the mind of the treating physician. An elevated plasma creatine kinase (CK) level is the most sensitive laboratory finding pertaining to muscle injury; whereas hyperkalaemia, acute renal failure and compartment syndrome represent the major life-threatening complications. The management of the condition includes prompt and aggressive fluid resuscitation, elimination of the causative agents and treatment and prevention of any complications that may ensue. The objective of this review is to describe the aetiological spectrum and pathophysiology of rhabdomyolysis, the clinical and biological consequences of this syndrome and to provide an appraisal of the current data available in order to facilitate the prevention, early diagnosis and prompt management of this condition.

KEYWORDS

Creatine kinase, rhabdomyolysis, muscle weakness, myoglobin, myoglobinuria

INTRODUCTION

Rhabdomyolysis is a potentially life-threatening syndrome characterised by the breakdown of skeletal muscle resulting in the subsequent release of intracellular contents into the circulatory system. These cell contents include enzymes such as creatine kinase (CK), glutamic oxalacetic transaminase, lactate dehydrogenase, aldolase, the haeme pigment myoglobin, electrolytes such as potassium and phosphates, and purines.[1-3] The development of rhabdomyolysis may be associated with a wide variety of diseases, injuries, medications and toxins. It ranges in severity from an asymptomatic elevation of CK levels in blood, to severe life-threatening cases associated with very high CK levels, myoglobinuria and acute renal failure.
Rhabdomyolysis was first reported in Germany in 1881, but it was Bywaters and Beall who described the syndrome in detail after the Battle of London, during the Second World War.[4]

PATHOPHYSIOLOGY

Although the causes of rhabdomyolysis are so diverse, the pathogenesis appears to follow a final common pathway, ultimately leading to myocyte destruction and release of muscle components into the circulation. In the normal myocyte, the sarcolemma, a thin membrane that encloses striated muscle fibres, contains numerous pumps that regulate cellular electrochemical gradients. The intercellular sodium concentration is normally maintained at 10 mEq/l by a sodium-potassium adenosine triphosphatase (Na/K-ATPase) pump located in the sarcolemma.[5] The Na/K-ATPase pump actively transports sodium from the interior of the cell to the exterior. As a result, the interior of the cell is more negatively charged than the exterior because positive charges are transported across the membrane. The gradient pulls sodium to the interior of the cell in exchange for calcium by a separate ion exchange channel. Moreover, low intracellular calcium levels are also maintained by an active calcium exchanger (Ca^{2+} ATPase pump) that promotes calcium entry into the sarcoplasmic reticulum and mitochondria.[6] The above processes depend on ATP as a source of energy. ATP depletion, which appears to be the end result of most causes of rhabdomyolysis, results in Na/K-ATPase and

Ca^{2+} ATPase pump dysfunction, the end result of which is an increased cellular permeability to sodium ions due to either plasma membrane disruption or reduced cellular energy (ATP) production.[7] Accumulation of sodium in the cytoplasm leads to an increase in intracellular calcium concentration (which is normally very low relative to the extracellular concentration). This excess calcium then increases the activity of intracellular proteolytic enzymes that degrade the muscle cell. As the myocyte degenerates, large quantities of potassium, aldolase, phosphate, myoglobin, CK, lactate dehydrogenase, aspartate transaminase and urate leak into the circulation.[5,7,8] Under physiological conditions, the plasma concentration of myoglobin is very low (0 to 0.003 mg per dl). If more than 100 g of skeletal muscle is damaged, the circulating myoglobin levels exceed the protein-binding capacity of the plasma and can precipitate in the glomerular filtrate. Excess myoglobin may thus cause renal tubular obstruction, direct nephrotoxicity, and acute renal failure.[9-11] *Figure 1* describes the mechanisms of rhabdomyolysis.

CAUSES

The aetiological spectrum of rhabdomyolysis is extensive; in many cases, multiple muscle insults are usually needed to produce rhabdomyolysis unless an underlying myopathy is present.[12] The most common causes of rhabdomyolysis in adults are illicit drugs, alcohol abuse, medical drugs, muscle diseases, trauma, neuroleptic malignant syndrome (NMS), seizures and immobility.[12] Whereas in paediatric patients, the most common causes are viral myositis, trauma, connective tissue disorders, exercise, and drug overdose.[11] *Table 1* summarises the causes of rhabdomyolysis.

Drugs and toxins

Rhabdomyolysis may result from substance abuse, toxins, prescription and nonprescription medications. Substances that are commonly abused include ethanol, methanol and ethylene glycol,[13,14] heroin,[15] methadone,[16] barbiturates,[17] cocaine,[18] caffeine,[19] amphetamine,[20] lysergic acid diethylamide,[21] 3,4-methylenedioxymethamphetamine

Figure 1. *Mechanisms of rhabdomyolysis*

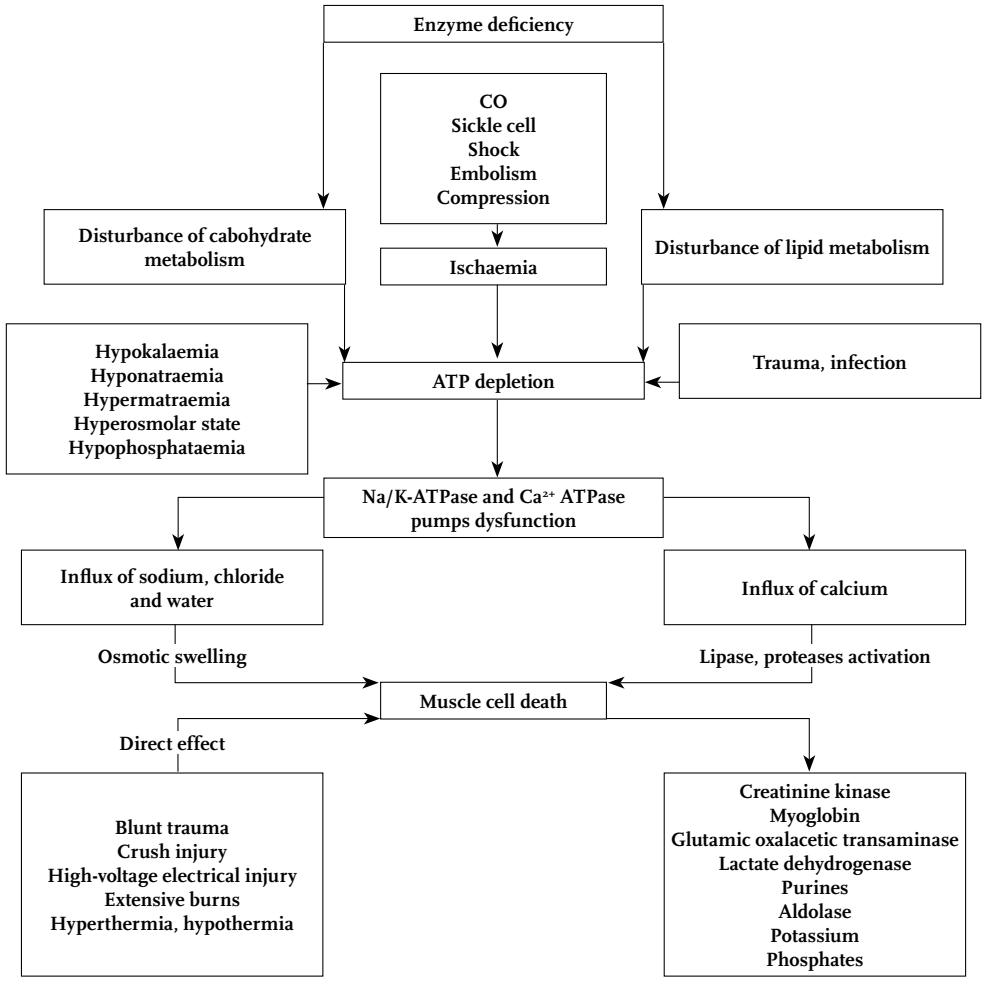

Table 1. *Causes of rhabdomyolysis*

Drugs and toxins
Trauma
Excessive muscular activity
Temperature extremes
Muscle ischaemia
Prolonged immobilisation
Infection
Electrolyte and endocrine abnormalities
Genetic disorders
Connective tissue disorders
Unknown

(MDMA, ecstasy),[22] phencyclidine,[23] benzodiazepines,[24] and toluene (from glue sniffing).[25]

Alcohol can induce rhabdomyolysis through a combination of mechanisms including immobilisation, direct myotoxicity and electrolyte abnormalities (hypokalaemia and hypophosphataemia).[9] Moreover cocaine-induced rhabdomyolysis may occur through multiple mechanisms: vasospasm with muscular ischaemia, seizures, hyperpyrexia, coma with muscle compression, and direct myofibrillar damage.[17]

Excessive use of barbiturates, benzodiazepines, and other sedative and hypnotics can cause depression of the central nervous system with prolonged immobilisation and muscle compression, resulting in muscle hypoxia and destruction.[26]

Other causes of toxin-induced rhabdomyolysis include carbon monoxide (CO),[27] hemlock herbs from quail,[9] snake bites,[28] spider venom (e.g., black widow spider),[29] and massive honey bee envenomations.[30] CO combines with haemoglobin to form carboxyhaemoglobin in the blood and prevents the binding of oxygen, so causing muscle hypoxia and rhabdomyolysis.

Rhabdomyolysis may also result from both prescribed and over-the-counter medications including[31] salicylates,[32], fibric acid derivatives (e.g., bezafibrate, clofibrate, fenofibrate, gemfibrozil),[33-36] neuroleptics,[37] anaesthetic and paralytic agents (the malignant hyperthermia syndrome),[38] quinine,[39] corticosteroids,[40] statins (e.g., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, cerivastatin),[41-46] theophylline,[47] cyclic antidepressants, selective serotonin reuptake inhibitors (the serotonin syndrome),[48] aminocaproic acid,[49] phenylpropanolamine,[50] and propofol.[51]

Statin-induced rhabdomyolysis may result from a variety of mechanisms. Firstly an unstable skeletal muscle cell membrane due to a blockage in the synthetic pathway for cholesterol, which results subsequently in a low intra-membranous cholesterol content. Secondly, the presence of abnormal prenylated protein causes an imbalance in intracellular protein messenger. Thirdly, abnormal mitochondrial respiratory function occurs which is caused by coenzyme Q10 deficiency.[44]

Trauma

Rhabdomyolysis may also occur after traumatic events, including significant blunt trauma (caused by physical assault or sudden automobile deceleration) or crush injuries,[52] high-voltage electrical injury (from lightning strikes or electrocution by high-voltage power supplies),[53] and extensive third-degree burns.[1]

Crush injuries are associated with severe trauma and most commonly occur with multiple casualty disasters, such as bombings, earthquakes, building collapse, mine accidents, and train accidents.[54-57] Rhabdomyolysis is actually noted to occur only once the acute compression of the muscle is relieved during which the necrotic muscle is released into the circulation: for example, once the victims of collapsed buildings are excavated or the people crushed during car accidents are released. In high-voltage electrical injury and extensive third-degree burns, rhabdomyolysis occurs through the direct myofibrillar damage that results as a consequence of the electrical insult.

Excessive muscular activity

Other significant causes of rhabdomyolysis include excessive muscular activity,[58-61] such as sporadic strenuous exercise (e.g., marathons), status epilepticus, status asthmaticus, severe dystonia, acute psychosis, and military recruits in boot camp. The more strenuous or prolonged the exercise, the more damage is incurred. Excessive muscular activity results in a state in which ATP production cannot keep up with the demand, subsequently exhausting cellular energy supplies leading to a disruption of muscle cell membranes. Factors that increase the risk of exertional rhabdomyolysis are hypokalaemia (often resulting from excessive sweating), and sickle-cell trait (especially in combination with high altitude), extreme heat and humidity, exercise-induced asthma, or pre-exertion fatigue.[62] Noteworthy, rhabdomyolysis cases associated with low-intensity exercise have also been reported.[63] In these cases the mechanism remains unknown.

Temperature extremes

Excess heat, regardless of its cause, may result in muscle damage. The term *thermal maximum* was developed to measure the magnitude and duration of heat that cells can endure before becoming damaged. Human *thermal maximum* has been established as a core body temperature of approximately 42 °C (107.6 °F) for between 45 minutes and eight hours.[64] Cellular destruction occurs more quickly and completely at higher temperatures. Causes of excess heat include heat stroke,[65] neuroleptic malignant syndrome[66] and malignant hyperthermia syndrome.[67] Although rare, exposure to cold with or without hypothermia can lead to rhabdomyolysis,[12,68,69] due to direct muscle injury.[70]

Muscle ischaemia

Muscle ischaemia interferes with oxygen delivery to the cells, thereby limiting the production of ATP. If oxygen deprivation is maintained for prolonged periods this may result in muscle cell necrosis. Skeletal muscle ischaemia may result from either localised or generalised conditions. Localised causes include compression of blood vessels[71-73] (e.g., intraoperative use of tourniquets, tight dressings or casts, prolonged application of air splints or pneumatic antishock garments and clamping of vessels during surgery), thrombosis, embolism, compartment syndrome, CO and sickle cell trait.[74,75] On the other hand, generalised causes of muscle ischaemia include hypotension and shock states.

Prolonged immobilisation

Prolonged immobilisation (e.g., anaesthesia, coma, drug or alcohol-induced unconsciousness) has been reported to cause rhabdomyolysis due to unrelieved pressure on gravity-dependent body parts.[76] As reported by Szewczyk *et al.*,[77] the most common positions leading to rhabdomyolysis were the lateral decubitus, lithotomy, sitting, knee-to-chest and prone position. The primary mechanism is reperfusion of damaged tissue after a period of ischaemia, and the release of necrotic muscle material into the circulation after pressure is relieved.[76,77] The risk factors for position-related rhabdomyolysis were identified as body weight more than 30% above ideal body weight, duration of surgery more than five to six hours, extracellular volume depletion, pre-existing azotaemia, diabetes, and hypertension.[78]

Infections

The proposed mechanisms for infection-induced rhabdomyolysis include tissue hypoxia (caused by sepsis, hypoxia, dehydration, acidosis, electrolyte disturbances and hypophosphataemia), direct bacterial invasion of muscle, low oxidative and glycolytic enzyme activity, activation of lysosomal enzymes and mechanisms implicating endotoxins.[79-81]

Numerous bacterial, viral, fungal and protozoal infections can lead to rhabdomyolysis. Viral infections as a cause of rhabdomyolysis have been described in many reports worldwide, of which influenza types A and B[82,83] are the most common. Other viruses linked towww rhabdomyolysis include HIV,[84] coxsackievirus,[85] Ebstein-Barr virus,[86] echovirus,[87] cytomegalovirus,[88] herpes simplex virus,[89] varicella-zoster virus,[90] and West Nile virus.[9W1]

Bacterial infections including *Legionella* species are classically associated with rhabdomyolysis in adults.[92] Other bacterial agents that might cause rhabdomyolysis include *Salmonella* species,[93] *Streptococci* species,[94,95] *Francisella tularensis*,[96] *Staphylococcus aureus*[97] *Leptospira* species,[98] *Mycoplasma* species[99] and *Escherichia coli*.[100]

On the other hand, rhabdomyolysis has been reported in patients with fungal and malaria infections.[101-103]

Electrolyte and endocrine abnormalities

Severe electrolyte derangements, including hyponatraemia,[104] hypernatraemia,[105] hypokalaemia[106] and hypophosphataemia[107] may lead to rhabdomyolysis, with the proposed mechanism being cell membrane disruption as a result of deranged sodium-potassium-ATPase pump function.

Endocrine abnormalities such as hypothyroidism[108] or hyperthyroidism,[109] diabetic ketoacidosis,[110] and non-ketotic hyperosmolar diabetic coma[111] have been reported to cause rhabdomyolysis.

Genetic disorders

These disorders usually start during childhood; a history of recurrent episodes of rhabdomyolysis, a family history of attacks or episodes precipitated by mild exertion or starvation increases the probability of a genetically determined metabolic myopathy. Inherited disorders that may cause rhabdomyolysis include enzyme deficiencies (of carbohydrate or lipid metabolism)[112,113] and myopathies.[114] Abnormalities in glycogen or lipid metabolism result in a block of anaerobic glycolysis that predisposes to the loss of integrity of the sarcolemmal membrane and the liberation of myoglobin following exercise. *Table 2* describes the common genetic disorders that cause rhabdomyolysis.

Table 2. *Common genetic disorders that cause rhabdomyolysis*

Deficiencies of glyco(geno)lytic enzymes
Myophosphorylase (McArdle's disease)
Phosphorylase kinase
Phosphofructokinase (Tarui's disease)
Phosphoglycerate mutase
Phosphoglycerate kinase
Lactate dehydrogenase
Abnormal lipid metabolism
Carnitine palmitoyltranferase deficiency I and II
Carnitine deficiency
Other genetic disorders
Myoadenylate deaminase deficiency
Duchenne's muscular dystrophy
Malignant hyperthermia

Connective tissue disorders

Although considered rare, it is known that connective tissue disorders such as polymyositis, dermatomyositis and Sjögren's syndrowwwme may induce rhabdomyolysis.[115-117]

Unknown causes

In many cases the aetiology of rhabdomyolysis cannot be identified. Some of these cases present with recurrent myoglobinuria and are termed idiopathic paroxysmal myoglobinuria (Meyer-Betz disease). Whether such patients have a genetic defect requires further study.

CLINICAL FEATURES

The clinical presentation is extremely variable; due to the large range of causes of this condition, it may vary from subclinical to severe, depending upon the extent and severity of muscle damage. Tea-coloured urine is a classical manifestation of rhabdomyolysis.

In conscious patients, the main complaint may be muscle tenderness, swelling, stiffness and cramping, accompanied by weakness and loss of function in the involved muscle group(s).[2,3,8,9] Muscle swelling may not become apparent until after rehydration with intravenous fluids. Most frequently the involved muscle groups are the postural muscles of the thighs, calves and lower back.[118] Nonspecific systemic symptoms, such as malaise, fever, abdominal pain, and nausea and vomiting, may also be seen.[3,8,9] Changes in mental status occur occasionally, either secondary to urea-induced encephalopathy or related to the underlying aetiology (e.g. toxins, infections, electrolyte disturbance, drugs and trauma). In comatose patients, the finding of limb induration may suggest rhabdomyolysis. Skin changes due to ischaemic tissue injury (discoloration, blisters) may be present on the affected area; however, there may be no signs of muscle involvement.

Rhabdomyolysis may be an incidental finding during laboratory testing, in such cases efforts should be directed toward finding the underlying aetiology.

INVESTIGATIONS

Unless there is a high index of suspicion, rhabdomyolysis can be missed, since muscular pain, swelling, and tenderness may not be prominent features and may even be absent. Therefore, the definitive diagnosis of rhabdomyolysis should be made by laboratory tests including serum CK and urine myoglobin. In addition, skeletal muscle biopsy can be used to confirm the diagnosis.

Serum creatine kinase

Serum CK concentration, mainly the CK-MM subtype, is the most sensitive indicator of damage to muscles. Serum CK begins to rise approximately 2 to 12 hours after the onset of muscle injury, peaks within 24 to 72 hours, and then declines at the relatively constant rate of 39% of the previous day's value.[118] A persistently elevated CK level suggests continuing muscle injury or development of a compartment syndrome.[119] Although various values of CK have been postulated to define rhabdomyolysis, the magnitude of elevation is rather arbitrary; and there is no cut-off value that conclusively diagnoses rhabdomyolysis. A serum CK activity greater than five times the normal value (in the absence of heart or brain diseases) was accepted by many authors as a criterion for the diagnosis of rhabdomyolysis.[1,2] However, the Clinical Advisory on Statins defined statin-induced rhabdomyolysis as muscle symptoms with marked CK elevation typically substantially greater than 10 times the upper limit of normal, with a creatinine elevation consistent with pigment nephropathy and usually with brown urine with myoglobinuria.[120,121]

Serum and urine myoglobin

Myoglobin is normally bound to plasma globulins, and has a rapid renal clearance which maintains a low plasma level up to a certain serum concentration (0 to 0.003 mg/dl). After the occurrence of muscle damage the circulating myoglobin levels exceed the plasma protein binding capacity, reach the glomeruli and are eventually excreted in the urine. Myoglobinuria does not occur without rhabdomyolysis, but rhabdomyolysis does not necessarily lead to visible myoglobinuria (tea or cola coloured urine). Before the urine becomes discoloured by myoglobin the level of myoglobin in the urine must exceed 100 mg/dl.[122] Although elevated serum myoglobin and myoglobinuria are reliable parameters for rhabdomyolysis, their sensitivity and specificity are affected by many factors. Firstly, serum myoglobin usually increases before a rise in CK and drops more rapidly than does the decline in CK concentration (in one to six hours).[119] Moreover, myoglobinuria may not be visible or may resolve early in the course of rhabdomyolysis. These facts make this parameter less sensitive and therefore should not be relied upon to rule out the diagnosis of rhabdomyolysis. Secondly, myoglobinuria is detected by urine dipstick tests (orthotoluidine), which also react with the globin fragment of haemoglobin. Thus, in the presence of red blood cells or haemolysis, the specificity of this test is limited. Radioimmunoassay is more sensitive and specific than dipstick. However, this test is often not readily available, and it may take more than 24 hours to obtain results.

Muscle biopsy

The muscle biopsy is not necessary, although it can be used to confirm the diagnosis of rhabdomyolysis. The histopathological findings usually include loss of cell nucleus and muscular stria with the absence of inflammatory cells.[123]

Investigations for underlying abnormalities

Once the diagnosis of rhabdomyolysis is established, a search must be instituted for a cause. A careful history and physical examination may reveal the underlying aetiology of rhabdomyolysis or at least may help in the selection of the appropriate diagnostic workup. However, in many cases the history and clinical examination are not conclusive; in such cases the decision to select the appropriate test is not clear since there is no standard protocol for such a situation. Actually, the nature of the investigations depends on the disorder suspected; thus, toxicological screens should be

performed if drugs are a suspected causal agent, whereas appropriate cultures and serological studies should be performed if infections are suspected. Endocrine assay and blood chemistry may be necessary to confirm the suspected endocrine and metabolic disorders. Furthermore, genetic analysis, muscle biopsy, and the forearm ischaemic test[124] may be indicated in patients with suspected genetic disorders, whereas the susceptibility of any individual to malignant hyperthermia can be detected by performing the Caffeine Halothane Contracture Test (CHCT).[125] Magnetic resonance image (MRI) may be useful in distinguishing the various aetiologies of rhabdomyolysis.[126,127]

Other investigations

Arterial blood gas analysis is useful tool to evaluate acid-base balance, whereas ECG is helpful to evaluate for cardiac arrhythmias related to hyperkalaemia or hypocalcaemia. Complete blood count including haemoglobin, haematocrit and platelets, blood chemistry, liver function tests, prothrombin time (PT), activated partial thromboplastin time (aPTT), serum aldolase, and lactate dehydrogenase are other useful laboratory tests that should be included. MRI is very effective in localising rhabdomyolysis, especially when fasciotomy is considered as a treatment option. The sensitivity of MRI in the detection of muscle involvement is higher than that of either computed tomography or ultrasound.[128]

Investigations may show hyperkalaemia, hypocalcaemia, hyperphosphataemia, hyperuricaemia, metabolic acidosis and raised levels of other muscle enzymes including lactate dehydrogenase, aldolase, carbonic anhydrase III and aminotransferases.[113] An elevated aspartate aminotransferase (with a normal alanine aminotransferase) could be a clue that rhabdomyolysis is occurring. The hypercalcaemia observed in some patients during the recovery phase of acute renal failure is due to the mobilisation of calcium from their muscle deposits and because of secondary hyperparathyroidism which usually occurs.[129] Troponin I was found to be high in 50% of patients with rhabdomyolysis. Of these, 58% were ultimately found to be true positives, 33% were false positives, and 9% were indeterminate.[130] Serum creatinine may be disproportionately elevated in relation to blood urea nitrogen in the absence of prerenal azotaemia, because of the release of preformed creatine from damaged muscles and its spontaneous hydration to creatinine.

COMPLICATIONS

The complications of rhabdomyolysis include hypovolaemia, compartment syndrome, arrhythmias, disseminated intravascular coagulation, hepatic dysfunction and acute renal failure. *Table 3* describes the complications of rhabdomyolysis.

Table 3. *Complications of rhabdomyolysis*

Hypovolaemia
Compartment syndrome
Arrhythmias and cardiac arrest
Disseminated intravascular coagulation
Hepatic dysfunction
Acidosis
Acute renal failure

Hypovolaemia

Necrosis along with inflammation results in the influx of fluid into the necrotic muscle and the accumulation of substantial amounts of fluid into the affected limbs (up to 10 litres per limb). The influx of extracellular fluids produces a 'third space' effect and as fluid is lost from the circulation, hypovolaemia and haemodynamic shock develop.[131]

Compartment syndrome

The ischaemic and oedematous muscle further raises intra-compartmental pressure potentiating a vicious cycle of continuing ischaemia.[122]

Most striated muscles are contained within rigid compartments formed by fasciae, bones, and other structures. High intra-compartmental pressure provokes additional damage and necrosis. This further muscle damage is manifested as the 'second wave phenomenon', the persistent elevation or rebound elevation in CK levels at 48 to 72 hours after the initial insult. Prolonged ischaemia and infarction of muscle tissue can result in replacement of muscle by inelastic fibrous tissue and severe contractures (Volkmann's contracture).[113]

The measurement of intramuscular pressure provides an objective parameter guiding the decision to perform fasciotomy. In non-hypotensive patients, this should be done when the intramuscular pressure exceeds 50 mmHg or if pressure values between 30 and 50 mmHg show no tendency to decrease after a maximum of six hours.[9]

Arrhythmias and cardiac arrest

One of the most characteristic electrolyte abnormalities induced by rhabdomyolysis is severe hyperkalaemia, especially in patients with acidaemia or oliguria. Hyperkalaemia can precipitate severe arrhythmias and cardiac arrest. Hypocalcaemia resulting from calcium deposition in necrotic muscle is another electrolyte disturbance that may lead to cardiac arrhythmias.[1,2] Moreover, hyperkalaemia coupled with hypocalcaemia can predispose to malignant cardiac arrhythmias.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) may complicate severe rhabdomyolysis and can result in haemorrhagic complications.[118] It probably results from the

activation of the clotting cascade by components released from the damaged muscles.

Hepatic dysfunction

Hepatic dysfunction occurs in approximately 25% of patients with rhabdomyolysis. Proteases released from injured muscle may be implicated in hepatic inflammation.[132]

Acidosis

Sulphur-containing proteins released in large amounts can lead to hydrogen and sulphate loads that overwhelm renal excretory mechanisms, resulting in an anion gap acidosis, which may be severe. Other causes of acidosis in the setting of rhabdomyolysis include lactic acidosis from ischaemia and the acidosis of uraemia.

Acute renal failure

Acute renal failure (ARF) develops in 33% of patients and is the most serious complication in the days following the initial presentation.[122] Factors known to contribute to rhabdomyolysis-induced ARF include hypovolaemia, acidosis or aciduria, tubular obstruction, and the nephrotoxic effects of myoglobin.

ARF occurs as a result of decreased circulating plasma volume which potentiates renal hypoperfusion (via renal vasoconstriction) and in the presence of acidic urine, myoglobin and uric acid precipitates and forms obstructive casts. At urinary pH below 5.6, myoglobin dissociates into ferrihaemate and globin. Ferrihaemate has a direct nephrotoxic effect which potentiates acute tubular necrosis, a form of ARF. In the absence of hypovolaemia and acid urine, myoglobin has a less nephrotoxic effect.[6,9] Various clinical factors are used to predict the risk of ARF, including serum CK, creatinine, potassium, and Ca^{2+}, as well as the urine myoglobin level, but no single parameter has been established.[133]

MANAGEMENT

There is a lack of level I evidence from which the best management plans for rhabdomyolysis may be derived. In fact, no randomised controlled trials of treatment have been conducted, and most evidence is based on retrospective clinical studies, case reports and animal models. Nevertheless important aspects of management include prompt and aggressive fluid resuscitation, the elimination of causative agents and the management and prevention of any complications that may arise. *Table 4* summarises the management plan for rhabdomyolysis.

Prehospital care

Because hypovolaemia is often present, normal saline (NS) resuscitation should be initiated preferably at the site of injury, before extrication. It has been reported that early intervention has decreased the incidence of ARF.[134] Intravenous access should immediately be secured with a large-bore catheter and normal saline infusion should begin at a rate of 1.5 litres/hour to maintain a urine output of 200 to 300 ml/hour. Potassium- or lactate-containing solutions should be avoided because of the risk of rhabdomyolysis-associated hyperkalaemia and lactic acidosis.

Table 4. *Management plan for patients with rhabdomyolysis*

Prehospital care
- ABC assessment
- Intravenous access
- Consider the importance of early fluid administration in the field
- NS infusion at a rate of 1.5 litres /hour, to maintain a urine output of 200-300 ml/hour
- Avoid empirical administration of potassium and lactate-containing fluids

Inhospital care
- Aggressive intravenous rehydration
- A careful history and physical examination
- Closely monitor serum electrolyte and CK
- Monitor fluid intake and urinary output (urinary catheter insertion).
- Check limbs for compartment syndromes
- Haemodynamic monitoring (central venous pressure measurements).
- Administer mannitol and bicarbonate (for patients with crush injury): a 20% mannitol infusion at a dose of 0.5 g/kg is given over a 15-minute period and subsequently followed by an infusion at 0.1 g/kg/h. Adjustments are made to maintain urine output >200 ml/h. Sodium bicarbonate, one ampoule (44 mEq) added to 1 l of ½NS or two to three ampoules (88 to 132 mEq) in D5W to run at a rate of 100 ml/hour, has been recommended to maintain a urinary pH of ≤6.5 to prevent the development of ARF
- Intensive care monitoring (for critically ill patients)

Treatment of any reversible cause of muscle damage
- Correct electrolyte and metabolic abnormalities
- Treat hyperthermia and hypothermia
- Eliminate and detoxify drugs and toxins

Management and prevention of complications
- Hyperkalaemia may be fatal and should be corrected vigorously
- Hypocalcaemia should be corrected only if it causes symptoms
- Hypophosphataemia and hyperphosphataemia usually require no treatment; treat hyperphosphataemia with oral phosphate binders when serum levels exceed 7 mg/dl
- Compartment syndrome requires immediate orthopaedic consultation for fasciotomy
- DIC usually resolves spontaneously after several days if the underlying cause is corrected, but if haemorrhagic complications occur, therapy with platelets, vitamin K, and fresh frozen plasma may be necessary
- Hyperuricaemia and hyperphosphataemia are rarely of clinical significance and rarely require treatment
- Consider dialysis as a lifesaving procedure for patients with rising or elevated potassium level, persistent acidosis, or oliguric renal failure with fluid overload
- Consider continuing dialysis support until patients' kidney function has recovered

CK = creatine kinese; ½NS = half-normal saline; D5W = dextrose 5%; ARF = acute renal failure; DIC = disseminated intravascular coagulation.

Inhospital care

Once in hospital, aggressive intravenous rehydration should be continued in order to promote vigorous diuresis and to dilute the released toxic products:[135] An infusion of 1.5 litres of saline per hour is often required during the initial management, and 300 to 500 ml/h once haemodynamic stability has been achieved. In severe cases of rhabdomyolysis with crush injury, administration of both blood products and normal saline may be necessary for the effective treatment of hypovolaemia.

Concurrently, a careful history and physical examination should be attempted in order to identify and manage any underlying illnesses. Vital signs, urine output, serial electrolyte levels, and CK levels should be obtained as soon as possible. Intensive care monitoring may be required depending on the severity of the clinical scenario. A urinary catheter should be inserted and urine output should be monitored carefully. For patients with heart disease, comorbid conditions, preexisting renal disease or for elderly patients, haemodynamic monitoring may be necessary to avoid fluid overload. Although there is no standard protocol in the literature for the duration of fluid administration, IV fluid should be continued until the levels of CK in the plasma decrease to 1000 U/l or below.[2]

Although there are no randomised controlled trials supporting this, the addition of mannitol and bicarbonate after the initial resuscitation with saline has been recommended (especially in crush injury) by many experts[136,137] to prevent acute kidney injury.

Proposed benefits of mannitol include an increase in the renal blood flow and glomerular filtration rate which may help to prevent obstruction by myoglobin casts; osmotic diuretics draw fluid in from the interstitial compartment to the intravascular compartment which counteracts the hypovolaemia and acts to reduce muscle swelling and nerve compression, as well as the scavenging of free radicals.[6,134,138,139]

Mannitol should only be given after volume replacement and avoided in patients with oliguria. A 20% mannitol infusion at a dose of 0.5 g/kg is given over a 15-minute period and subsequently followed by an infusion at 0.1 g/kg/h. Adjustments are made to maintain urine output at >200 ml/h. Urinary and serum pH levels are monitored, with acetazolamide added if the serum pH is >7.45 or urinary pH remains <6.0.[133] The use of loop diuretics (e.g., furosemide) in rhabdomyolysis is controversial, with some researchers recommending their use and others opposing it because loop diuretics acidify the urine.[118]

Alkalinisation of urine (by sodium bicarbonate) is advocated for the purpose of decreasing cast formation, minimising the toxic effects of myoglobin on the renal tubules, inhibiting lipid peroxidation, and decreasing the risk for hyperkalaemia. Sodium bicarbonate, one ampoule (44 mEq) added to 1 litre of half-normal saline (½NS) or two to three ampoules (88 to 132 mEq) in dextrose 5% (D5W) to run at a rate of 100 ml/h, has been recommended to maintain a urine pH of ≥6.5 to prevent the development of ARF.[140]

Treatment of any reversible cause of muscle damage

In order to stop ongoing muscle destruction any underlying condition, such as trauma, infection, or toxins, must obviously be identified and treated as soon as possible. Treatment of hyperthermia is essential and can be achieved by using external cooling measures and by controlling for muscular hyperactivity with benzodiazepines. In malignant hyperthermia, anaesthetics should be discontinued, and the patient should be treated with dantrolene sodium; the usual initial dose is 2.5 to 4.0 mg/kg, followed by about 1 mg/kg every four hours for up to 48 hours to avoid recrudescence. Electrolyte and metabolic abnormalities that cause rhabdomyolysis (e.g., hyponatraemia, hypernatraemia, hyperglycaemia, hypercalcaemia, and decreased phosphorous) should be corrected promptly. Drugs and toxins should be eliminated and detoxified (e.g., gastric lavage, antidotes and/or haemodialysis) if possible, and hypoxia must be corrected.

Management and prevention of complications

Aggressive rehydration is considered the standard of care in preventing ARF in patients with rhabdomyolysis, while the role of mannitol and bicarbonate is controversial. In 1984, Ron *et al.*[141] published a review of seven patients treated for crush injuries suffered after the collapse of a building. Mannitol and sodium bicarbonate were used over the first five days. Visible myoglobinuria cleared at an average of 48 hours and at no time did patients have a creatinine of >1.5 mg/dl and none of the patient required haemodialysis. But lack of a control group is the major limitation of this study. In an experimental study conducted in 2005, Ozguc *et al.*[142] reported that the association of saline solution, sodium bicarbonate, and mannitol was more effective than hypertonic saline-dextran in decreasing oxidant injury in rhabdomyolysis; they also found that hypertonic saline-dextran increased metabolic acidosis that followed autologous muscle extract infusion. Other experimental studies by Zagar in 1992[143] suggested that mannitol may be protective due to the associated diuresis that minimises intratubular haeme pigment deposition.

In 1994, Knottenbelt[56] published a retrospective review of 200 patients with extensive soft tissue injuries from severe beatings, who received fluid loading with balanced salt solution (without mannitol or bicarbonate). He found that significantly increased rates of ARF and death were associated with injury-admission intervals of more than 12 hours, severe metabolic acidosis, low initial haemoglobin, heavy pigmenturia, and high serum CK levels. Accordingly, large-volume infusion of crystalloid alone creates a solute diuresis sufficient to alkalinise the urine.

In 1997, Homsi *et al.* performed a retrospective analysis of patients with rhabdomyolysis at risk for ARF; they compared groups receiving saline (n=9) *vs* saline, bicarbonate and mannitol (n=15). The authors concluded that progression to established renal failure can be totally avoided with prophylactic treatment, and that once appropriate saline expansion is provided, the association of mannitol and bicarbonate seems to be unnecessary.[144] In 2004, Brown *et al.* found that the use of sodium bicarbonate and mannitol in post-traumatic rhabdomyolysis does not prevent ARF, dialysis or mortality in patients with CK levels >5000 U/l.[145] The author advised to reevaluate the standard of administering bicarbonate and mannitol to patients with post-traumatic rhabdomyolysis.

Based on this literature review and taking into consideration that sodium bicarbonate can aggravate hypocalcaemia, as well as contributing to a hyperosmolar state,[133] it can be concluded that, in patients with rhabdomyolysis and a good urinary response to fluid administration, alkalinisation of the urine with sodium bicarbonate and diuresis with mannitol is unnecessary and needs to be re-evaluated.

In animal models, free-radical scavengers (e.g., antioxidants) and iron chelators (e.g., deferoxamine) have been observed to minimise the renal damage caused by free radicals as well as the direct toxic effects of myoglobin, but their potential role in preventing ARF in patients with rhabdomyolysis is under investigation.

Rhabdomyolysis-induced ARF may be oliguric (most common) or nonoliguric. The need for dialysis, serum potassium and calcium levels, and mortality rates appear to be similar for rhabdomyolysis-induced and non-rhabdomyolysis-induced ARF. Patients with rhabdomyolysis-induced ARF, however, have higher serum uric acid and anion gap levels.[118]

Hyperkalaemia is a potentially life-threatening complication of rhabdomyolysis especially when associated with ARF and hypocalcaemia. Treatment should be initiated to prevent cardiac complications. Traditional insulin and glucose therapy is recommended. Intravenous calcium may be ineffective as a treatment for hyperkalaemia if given to a patient with hyperphosphataemia. This is because calcium and phosphate can combine and precipitate removing them from the circulation.[3] The use of ion-exchange resins (e.g., sodium polystyrene sulphonate) is effective but will take many hours. If hyperkalaemia persists despite these treatments, emergent dialysis will become a pertinent option.

Hypocalcaemia observed early in rhabdomyolysis usually requires no treatment. Calcium should only be given to treat hyperkalaemia-induced cardiotoxicity or profound signs and symptoms of hypocalcaemia. In contrast, hypercalcaemia is frequently symptomatic and normally responds to saline diuresis and intravenous furosemide. Hyperphosphataemia should be treated with oral phosphate binders when serum levels exceed 7 mg/dl. Similarly, the hypophosphataemia, which may occur late in rhabdomyolysis, requires treatment only when the serum level is below 1 mg/dl.

Compartment syndrome requires immediate orthopaedic consultation for fasciotomy. DIC usually resolves spontaneously after several days if the underlying cause is corrected, but if haemorrhagic complications occur, therapy with platelets, vitamin K, and fresh frozen plasma may be necessary.

Hyperuricaemia and hyperphosphataemia are rarely of clinical significance and rarely require treatment.

Metabolic acidosis should be treated with aggressive intravenous fluid hydration. Bicarbonate administration may be detrimental, as metabolic alkalosis could worsen the hypocalcaemia.

Dialysis should be considered as a lifesaving procedure for patients with rising or elevated potassium level, persistent acidosis, or oliguric renal failure with fluid overload. Dialysis with supportive care effectively limits the morbidity and mortality from ARF associated with rhabdomyolysis.

PROGNOSIS

The prognosis of rhabdomyolysis is heavily dependent upon the underlying aetiology and the associated comorbidities. Despite the lack of any well-organised prospective studies, the available evidence from case reports and small retrospective studies suggests that rhabdomyolysis, when treated early and aggressively, has an excellent prognosis. Moreover, the prognosis for the recovery of full renal function is also excellent.

REFERENCES

1. Sauret JM, Marinides G, Wang GK. Rhabdomyolysis. Am Fam Phys. 2002;65:907-12.
2. Lane R, Philps M. Rhabdomyolysis has many causes, including statins, and may be fatal. BMJ. 2003;327:115-6.
3. Visweswaran P, Guntupalli J. Rhabdomyolysis. Crit Care Clin. 1999;15:415-28.
4. Bywaters EGL, Beall D. Crush injuries with impairment of renal function. BMJ. 1941;1:427.
5. Luck RP, Verbin S. Rhabdomyolysis review of clinical presentation, etiology, diagnosis and management. Pediatr Emerg Care. 2008;24:262-8.
6. Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. Kidney Int. 1996;49:314-26.
7. Knochel JP. Mechanisms of rhabdomyolysis. Curr Opin Rheumatol. 1993;5:725-31.
8. Huerta-Alardín AL, Varon J, Marik PE. Bench-to-bedside review: Rhabdomyolysis - an overview for clinicians. Crit Care. 2005;9:158-69.
9. Vanholder R, Sever MS, Erek E, Lameire N. Rhabdomyolysis. J Am Soc Nephrol. 2000;11:1553-61.

10. Paller MS. Hemoglobin- and myoglobin-induced acute renal failure in rats: role of iron in nephrotoxicity. Am J Physiol. 1988;255(3 Pt 2):F539-44.

11. Mannix R, Tan ML, Wright R, Baskin M. Acute pediatric rhabdomyolysis: causes and rates of renal failure. Pediatrics. 2006;118:2119-25.

12. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore). 2005;84:377-85.

13. Bessa O. Alcoholic rhabdomyolysis: a review. Conn Med. 1995;59:519-21.

14. Deighan CJ, Wong KM, McLaughlin KJ, Harden P. Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse. QJM. 2000;93:29-33.

15. Klock JC, Sexton MJ. Rhabdomyolysis and acute myoglobinuric renal failure following heroin use. Calif Med. 1973;119:5-8.

16. Hojs R, Sinkovic A. Rhabdomyolysis and acute renal failure following methadone abuse. Nephron. 1992;62:362.

17. Crowe AV, Howse M, Bell GM, Henry JA. Substance abuse and the kidney. QJM. 2000;93:147-52.

18. Horowitz BZ, Panacek EA, Jouriles NJ. Severe rhabdomyolysis with renal failure after intranasal cocaine use. J Emerg Med. 1997;15:833-7.

19. Wrenn KD, Oschner I. Rhabdomyolysis induced by a caffeine overdose. Ann Emerg Med. 1989;18(1):94-7.

20. Terada Y, Shinohara S, Matui N, Ida T. Amphetamine-induced myoglobinuric acute renal failure. Jpn J Med. 1988;27(3):305-8.

21. Coco TJ, Klasner AE. Drug-induced rhabdomyolysis. Curr Opin Pediatr. 2004;16:206-10.

22. Dar KJ, McBrien ME. MDMA induced hyperthermia: a report of a fatality and review of current therapy. Intensive Care Med 1996;22:995-6.

23. Hoogwerf B, Kern J, Bullock M, Comty CM. Phencyclidine-induced rhabdomyolysis and acute renal failure. Clin Toxicol. 1979;14(1):47-53.

24. Baumgart U, Schmid R, Spiessl H. Olanzapine-induced acute rhabdomyolysis-a case report. Pharmacopsychiatry. 2005;38:36-7.

25. Karmakar GC, Roxburgh R. Rhabdomyolysis in a glue sniffer. N Z Med J. 2008 ;121:70-1.

26. Prendergast BD, George CF: Drug- induced rhabdomyolysis: Mechanisms and management. Postgrad Med J. 1993;69:333-6.

27. Sungur M, Güven M. Rhabdomyolysis due to carbon monoxide poisoning. Clin Nephrol. 2001;55:336-7.

28. Sitprija V. Snakebite nephropathy. Nephrology (Carlton). 2006;11:442-8.

29. Cohen J, Bush S. Case report: compartment syndrome after a suspected black widow spider bite. Ann Emerg Med. 2005;45:414-6.

30. Betten DP, Richardson WH, Tong TC, Clark RF. Massive honey bee envenomation-induced rhabdomyolysis in an adolescent. Pediatrics. 2006;117:231-5.

31. Khosla U, Ruel KS, Hunt DP. Antihistamine-induced rhabdomyolysis. South Med J. 2003;96:1023-6.

32. Montgomery H, Porter JC, Bradley RD. Salicylate intoxication causing a severe systemic inflammatory response and rhabdomyolysis. Am J Emerg Med. 1994;12:531-2.

33. Terrovitou CT, Milionis HJ, Elisaf MS. Acute rhabdomyolysis after bezafibrate re-exposure. Nephron. 1998;78(3):336-7.

34. Smals AG, Beex LV, Kloppenborg PW. Clofibrate-induced muscle damage with myoglobinuria and cardiomyopathy. N Engl J Med. 1977 21;296:942.

35. Tahmaz M, Kumbasar B, Ergen K, Ure U, Karatemiz G, Kazancioglu R. Acute renal failure secondary to fenofibrate monotherapy-induced rhabdomyolysis. Ren Fail. 2007;29:927-30.

36. Magarian GJ, Lucas LM, Colley C. Gemfibrozil-induced myopathy. Arch Intern Med. 1991;151(9):1873-4.

37. Khan FY, Qusad MJ. Neuroleptic malignant syndrome. Neurosciences. 2006;11:104-6.

38. Pedrozzi NE, Ramelli GP, Tomasetti R, Nobile-Buetti L, Bianchetti MG. Rhabdomyolysis and anesthesia: a report of two cases and review of the literature. Pediatr Neurol. 1996;15:254-7.

39. Lim AK, Ho L, Levidiotis V. Quinine-induced renal failure as a result of rhabdomyolysis, haemolytic uraemic syndrome and disseminated intravascular coagulation. Intern Med J. 2006;36:465-7.

40. Gayan-Ramirez G, Decramer M. The effect of corticotherapy on respiratory muscles. Rev Mal Respir. 1998;15:33-41.

41. Jose J, Saravu K, Shastry BA. Atorvastatin-induced early-onset rhabdomyolysis in a patient with nephrotic syndrome. Am J Health Syst Pharm. 2007;64(7):726-9.

42. Sylvain-Moore H, Worden JP. Lovastatin-induced rhabdomyolysis. Heart Lung. 1991;20:464-6.

43. Rosenberg AD, Neuwirth MG, Kagen LJ, Singh K, Fischer HD, Bernstein RL. Intraoperative rhabdomyolysis in a patient receiving pravastatin, a 3-hydroxy-3-methyglutaryl coenzyme A (HMG Co A) reductase inhibitor. Anesth Analg. 1995;81:1089-91.

44. Khan FY, Ibrahim W. Rosuvastatin induced rhabdomyolysis in a low risk patient: a case report and review of the literature. Curr Clin Pharmacol. 2009;4:1-3.

45. Bizarro N, Bagolin E, Milani L, Cereser C, Finco B. Massive rhabdomyolysis and simvastatin (letter). Clin Chem. 1992;38:1504.

46. Bakri R, Wang J, Wierzbicki AS, Goldsmith D. Cerivastatin monotherapy-induced muscle weakness, rhabdomyolysis and acute renal failure. Int J Cardiol. 2003;91:107-9.

47. Teweleit S, Hippius M, Pfeifer R, Hoffmann A. Rhabdomyolysis as a rare complication of theophylline poisoning. Med Klin (Munich). 2001;96:40-4.

48. Richards S, Umbreit JN, Fanucchi MP, Giblin J, Khuri F. Selective serotonin reuptake inhibitor-induced rhabdomyolysis associated with irinotecan. South Med J. 2003;96:1031-3.

49. Seymour BD, Rubinger M. Rhabdomyolysis induced by epsilon-aminocaproic acid. Ann Pharmacother. 1997;31:56-8.

50. Blewitt GA, Siegel EB. Renal failure, rhabdomyolysis, and phenylpropanolamine. JAMA. 1983;249:3017-8.

51. Casserly B, O'Mahony E, Timm EG, Haqqie S, Eisele G, Urizar R. Propofol infusion syndrome: an unusual cause of renal failure. Am J Kidney Dis. 2004;44:e98-101.

52. Malinoski DJ, Slater MS, Mullins RJ. Crush injury and rhabdomyolysis. Crit Care Clin. 2004;20:171-92.

53. Brumback RA, Feeback DL, Leech RW. Rhabdomyolysis following electrical injury. Semin Neurol. 1995;15:329-34.

54. Jones R. Crush syndrome in a Cornish tin mine. Injury. 1984;15:282.

55. Bentley G, Jeffereys T. The crush syndrome in coal miners. J Bone Joint Surg Br. 1968;50:588-94.

56. Knottenbelt JD. Traumatic rhabdomyolysis from severe beating - experience of volume diuresis in 200 patients. J Trauma. 1994;37:214-9.

57. Sever MS, Erek E, Vanholder R, et al. The Marmara earthquake: epidemiological analysis of the victims with nephrological problems. Kidney Int. 2001;60(3):1114-23.

58. Chugh KS, Singhal PC, Khatri GK. Rhabdomyolysis and renal failure following status asthmaticus. Chest. 1978;73(6):879-80.

59. Sharma N, Winpenny H, Heymann T. Exercise induced rhabdomyolysis: even the fit may suffer. Int J Clin Pract. 1999;53:476-7.

60. Singhal PC, Chugh KS, Gulati DR. Myoglobinuria and renal failure after status epilepticus. Neurology. 1978;28(2):200-1.

61. Coryell W, Norby LH, Cohen LH. Psychosis-induced rhabdomyolysis. Lancet. 1978;2:381-2.

62. Harrelson GL, Fincher AL, Robinson JB. Acute exertional rhabdomyolysis and its relationship to sickle cell trait. J Athl Train. 1995;4:309-12.

63. Gagliano M, Corona D, Giuffrida G, et al. Low-intensity body building exercise induced rhabdomyolysis: a case report. Cases J. 2009;2:7.

64. Bynum GD, Pandolf KB, Schuette WH, et al. Induced hyperthermia in sedated humans and the concept of critical thermal maximum. Am J Physiol. 1978;235:R228-36.

65. Bouchama A, Knochel JP. Heatstroke. N Engl J Med. 2002;346:1978-88.

66. Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. Br J Anaesth. 2000;85:129-35.

67. Girard T, Suhner M, Levano S, Singer M, Zollinger A, Hofer CK. A fulminant malignant hyperthermia episode in a patient with ryanodine receptor gene mutation p.Tyr522Ser. Anesth Analg. 2008;107:1953-5.

68. Aslam AF, Aslam AK, Vasavada BC, Khan IA. Hypothermia: evaluation, electrocardiographic manifestations, and management. Am J Med. 2006;119(4):297-301.

69. Korantzopoulos P, Papaioannides D, Sinapidis D, et al. Acute rhabdomyolysis due to prolonged exposure to the cold. Int J Clin Pract. 2003;57:243-4.

70. Lewis RB, Moen PW. Further studies on the pathogenesis of cold-induced muscle necrosis. Surg Gynecol Obstet. 1952;95:543-51.

71. Williams J, Tucker D, Read J. Rhabdomyolysis- myoglobinuria: consequences of prolonged tourniquet. J Foot Surg. 1983;22:52-6.

72. Salvian A J; Shackleton C R. Crush syndrome complicating pneumatic antishock garment (PASG) use. Injury. 1988;19:43-4.

73. Adiseshiah M, Round JM, Jones DA: Reperfusion injury in skeletal muscle: A prospective study in patients with acute limb ischemia and claudication treated by revascularization. Br J Surg. 1992;79:1026-9.

74. Slater MS, Mullins RJ. Rhabdomyolysis and myoglobinuric renal failure in trauma and surgical patients: a review. J Am Coll Surg. 1998;186:693-716.

75. George C, Brun-Bruisson C, Amamou M, LeGall JR. Acute renal failure due to rhabdomyolysis in sickle cell trait. Intensive Care Med. 1979;2:204-5.

76. Penn AS, Rowland LP, Fraser DW. Drugs, coma and myoglobinuria. Arch Neurol. 1972;26:336-43.

77. Szewczyk D, Ovadia P, Abdullah F, et al. Pressure induced rhabdomyolysis and acute renal failure. J Trauma. 1998;44:384.

78. Biswas S, Gnanasekaran I, Ivatury RR, et al. Exaggerated lithotomy position-related rhabdomyolysis. Am Surg. 1997;63:361-4.

79. Friman G, Ilback NG, Beisel WR. Effects of Streptococcus pneumoniae, Salmonella typhimurium and Francisella tularensis on oxidative, glycolytic, and lysosomal enzyme activity in red and white skeletal muscle in the rat. Scand J Infect Dis. 1984;16:111-9.

80. Blanco JR, Zabalza M, Salcedo J, Echeverria L, Garcia A, Vallejo M. Rhabdomyolysis of infectious and non-infectious causes. South Med J. 2002;95:542-4.

81. Brncic N, Viskovic I, Sasso A, Kraus I, Zamolo G. Salmonella infection-associated acute rhabdomyolysis. Some pathogenic considerations. Arch Med Res. 2002;33:313-5.

82. Swaringen JC, Seiler JG 3rd, Bruce RW Jr. Influenza A induced rhabdomyolysis resulting in extensive compartment syndrome. Clin Orthop Relat Res. 2000;(375):243-9.

83. Paletta CE, Lynch R, Knutsen AP. Rhabdomyolysis and lower extremity compartment syndrome due to influenza B virus. Ann Plast Surg. 1993;30:272-3.

84. Peraldi MN, Maslo C, Akposso K, Mougenot B, Rondeau E, Sraer JD. Acute renal failure in the course of HIV infection: a single-institution retrospective study of ninety-two patients and sixty renal biopsies. Nephrol Dial Transplant. 1999;14:1578-85.

85. Wang YM, Zhang Y, Ye ZB. Rhabdomyolysis following recent severe coxsackie virus infection in patient with chronic renal failure: one case report and a review of the literature. Ren Fail. 2006;28:89-93.

86. Osamah H, Finkelstein R, Brook JG. Rhabdomyolysis complicating acute Epstein-Barr virus infection. Infection. 1995;23:119-20.

87. Tanaka T, Takada T, Takagi D, Takeyama N, Kitazawa Y. Acute renal failure due to rhabdomyolysis associated with echovirus 9 infection: a case report and review of literature. Jpn J Med. 1989;28(2):237-42.

88. Wong WM, Wai-Hung Shek T, Chan KH, Chau E, Lai KC. Rhabdomyolysis triggered by cytomegalovirus infection in a heart transplant patient on concomitant cyclosporine and atorvastatin therapy. J Gastroenterol Hepatol. 2004;19(8):952-3.

89. Shanmugam S, Seetharaman M. Viral rhabdomyolysis. South Med J. 2008;101(12):1271-2.

90. Will MJ, Hecker RB, Wathen PI. Primary varicella-zoster-induced rhabdomyolysis. South Med J. 1996;89(9):915-20.

91. Gupta M, Ghaffari M, Freire AX. Rhabdomyolysis in a patient with West Nile encephalitis and flaccid paralysis. Tenn Med. 2008;101(4):45-7.

92. Erdogan H, Yilmaz A, Kal O, Erdogan A, Arslan H. Rhabdomyolysis-induced acute renal failure associated with legionnaires' disease. Scand J Urol Nephrol. 2006;40(4):345-6.

93. Khan FY, Al-Ani A, Ali HA. Typhoid rhabdomyolysis with acute renal failure and acute pancreatitis: a case report and review of the literature. Int J Infect Dis. 2009;13(5):e282-5.

94. Ojukwu IC, Newton DW, Luque AE, Kotb MY, Menegus M. Invasive Group C Streptococcus infection associated with rhabdomyolysis and disseminated intravascular coagulation in a previously healthy adult. Scand J Infect Dis. 2001;33(3):227-9.

95. Blanco JR, Zabalza M, Salcedo J, San Román J. Rhabdomyolysis as a result of Streptococcus pneumoniae: report of a case and review. Clin Microbiol Infect. 2003;9(9):944-8.

96. Kaiser AB, Rieves D, Price AH, et al. Tularemia and rhabdomyolysis. JAMA. 1985;253(2):241-3.

97. Lannigan R, Austin TW, Vestrup J. Myositis and rhabdomyolysis due to Staphylococcus aureus septicemia. J Infect Dis. 1984;150(5):784.

98. Coursin DB, Updike SJ, Maki DG. Massive rhabdomyolysis and multiple organ dysfunction syndrome caused by leptospirosis. Intensive Care Med. 2000;26(6):808-12.

99. Berger RP, Wadowksy RM. Rhabdomyolysis associated with infection by Mycoplasma pneumoniae: A case report. Pediatrics. 2000;105(2):433-6.

100. Henrich WL, Prophet D, Knochel JP. Rhabdomyolysis associated with Escherichia coli. South Med J. 1980;73(7):936-7.

101. Bedry R, Baudrimont I, Deffieux G, et al. Wild-Mushroom Intoxication as a Cause of Rhabdomyolysis. N Engl J Med. 2001;345(11):798-802.

102. Hinds SW, Rowe JM. Extreme rhabdomyolysis in a patient with acute leukemia. Association with Candida kruseii fungemia. N Y State J Med. 1988;88(11):599-600.

103. Sinniah R, Lye W. Acute renal failure from myoglobinuria secondary to myositis from severe falciparum malaria. Am J Nephrol. 2000;20(4):339-43.

104. Strachan P, Prisco D, Multz AS. Recurrent rhabdomyolysis associated with polydipsia-induced hyponatremia - a case report and review of the literature. Gen Hosp Psychiatry. 2007;29(2):172-4.

105. Incecik F, Herguner MO, Yildizdas D, et al. Rhabdomyolysis caused by hypernatremia. Indian J Pediatr. 2006;73:1124-6.

106. Agrawal S, Agrawal V, Taneja A. Hypokalemia causing rhabdomyolysis resulting in life-threatening hyperkalemia. Pediatr Nephrol. 2006;21:289-91.

107. Knochel JP, Barcenas C, Cotton JR, Fuller TJ, Haller R, Carter NW. Hypophosphatemia and Rhabdomyolysis. J Clin Invest. 1978;62(6):1240-6.

108. Kisakol G, Tunc R, Kaya A. Rhabdomyolysis in a patient with hypothyroidism. Endocr J. 2003;50:221-3.

109. Lichtstein DM, Arteaga RB. Rhabdomyolysis associated with hyperthyroidism. Am J Med Sci. 2006;332:103-5.

110. Kuo TS, Jap TS, Kwok CF, Ho LT. Severe rhabdomyolysis induced acute renal failure, caused by diabetic ketoacidosis. Zhonghua Yi Xue Za Zhi. 1990;46:311-4.

111. Ka T, Takahashi S, Tsutsumi Z, Moriwaki Y, Yamamoto T, Fukuchi M. Hyperosmolar non-ketotic diabetic syndrome associated with rhabdomyolysis and acute renal failure: a case report and review of literature. Diabetes Nutr Metab. 2003;16:317-22.

112. Lofberg M, Jankala H, Paetau A, Harkonen M, Somer H. Metabolic causes of recurrent rhabdomyolysis. Acta Neurol Scand. 1998;98:268-75.

113. Poels PJE, Gabreels FJM. Rhabdomyolysis: a review of the literature. Clin Neurol Neurosurg. 1993;95:175-92.

114. Brumback RA, Feeback DL, Leech RW. Rhabdomyolysis in childhood. A primer on normal muscle function and selected metabolic myopathies characterized by disordered energy production. Pediatr Clin North Am. 1992;39:821-58.

115. Kim HW, Choi JR, Jang SJ, Chang YS, Bang BK, Park CW. Recurrent rhabdomyolysis and myoglobinuric acute renal failure in a patient with polymyositis. Nephrol Dial Transplant. 2005;20:2255-8.

116. Caccamo DV, Keene CY, Durham J, Peven D. Fulminant rhabdomyolysis in a patient with dermatomyositis. Neurology. 1993;43:844-5.

117. Prakash EBS, Fernando ME, Sathiyasekaran M, Bhoopathy RM, Jayanth JJ. Primary Sjögren's syndrome presenting with distal renal tubular acidosis and rhabdomyolysis. JPI. 2006;54:949-50.

118. Tintinalli JE, Kelen GD, Stapczynski JS. Emergency medicine: A comprehensive study guide. 6th ed. New York: McGraw-Hill Inc; 2004.

119. Minnema BJ, Neligan PC, Quraishi NA, Fehlings MG, Prakash S. A case of occult compartment syndrome and nonresolving rhabdomyolysis. J Gen Intern Med. 2008;23:871-4.

120. Anton KA, Williams CD, Baker SK, Philips PS. Clinical perspectives of statin-induced rhabdomyolysis. Am J Med. 2006;119:400-9.

121. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI Clinical advisory on the use and safety of statins. Stroke. 2002;33:2337-41.

122. Gabow PA, Kaehney WD, Kelleher SP. The spectrum of rhabdomyolysis. Medicine. 1982;61:141-9.

123. Hino I, Akama H, Furuya T. Pravastatininduced rhabdomyolysis in a patient with mixed connective tissue disease. Arthritis Rheum. 1996;39(7):1259.

124. Valen PA, Nakayama DA, Veum J, Sulaiman AR, Wortmann L. Myoadenylate deaminase deficiency and forearm ischemic exercise testing. Arthritis Rheum. 1987;30:661-8.

125. Rosenberg H, Antognini JF, Muldoon S. Testing for malignant hyperthermia. Anesthesiology. 2002;96:232-7.

126. Moratalla MB, Braun P, Fornas GM. Importance of MRI in the diagnosis and treatment of rhabdomyolysis. Eur J Radiol. 2008;65:311-5.

127. Beese MS, Winkler G, Maas R, Bucheler E. [MRI of musculature in myalgia--indications and image findings]. Aktuelle Radiol. 1996;6:119-29.

128. Kakuda W, Naritomi H, Miyashita K, et al: Rhabdomyolysis lesions showing magnetic resonance contrast enhancement. J Neuroimaging. 1999;9:182.

129. Sperling LS, Tumllin JA. Delayed hypercalcaemia after rhabdomyolysis induced acute renal failure. Am J Med Sci. 1996;311:186-8.

130. Li SF, Zapata J, Tillem E. The prevalence of false-positive cardiac troponin I in ED patients with rhabdomyolysis. Am J Emerg Med. 2005;23:860-3.

131. Better OS. The crush syndrome revisited 1940-1990. Nephron. 1990;55:97-103.

132. Akmal M, Massry SG. Reversible hepatic dysfunction associated with rhabdomyolysis. Am J Nephrol. 1990;10:49-52.

133. O'Connor FG, Deuster PA. Rhabdomyolysis. In: Goldman L, Ausiello D, (eds). Cecil Medicine. Oxford: Elsevier-Saunders, 23rd ed, 2007.

134. Gunal AI, Celiker H, Dogukan A, et al. Early and vigorous fluid resuscitation prevents acute renal failure in the crush victims of catastrophic earthquakes. J Am Soc Nephrol. 2004;15:1862-7.

135. Allison RC, Bedsole DL. The other medical causes of rhabdomyolysis. Am J Med Sci. 2003;326(2):79-88.

136. Altintepe L, Guney I, Tonbul Z, et al. Early and intensive fluid replacement prevents acute renal failure in the crush cases associated with spontaneous collapse of an apartment in Konya. Ren Fail. 2007;29:737-41.

137. Better OS, Rubinstein I: Management of shock and acute renal failure in casualties suffering from the crush syndrome. Renal Fail. 1997;19:647-53.

138. Curry S, Chang D, Connor D. Drug and toxin-induced rhabdomyolysis. Ann Emerg Med. 1989;18:1068-84.

139. Odeh M. The role of reperfusion-induced injury in the pathogenesis of the crush syndrome. N Engl J Med. 1991;324:1417-22.

140. Malik GH. Rhabdomyolysis and Myoglobin-induced Acute Renal Failure. Saudi J Kidney Dis Transpl. 1998;9:273-84.

141. Ron D, Taitelman U, Michaelson M, et al. Prevention of acute renal failure in traumatic rhabdomyolysis. Arch Intern Med. 1984;144:277-80.

142. Ozguc H, Kahveci N, Akkose S, Serdar Z, Balci V, Ocak O. Effects of different resuscitation fluids on tissue blood flow and oxidant injury in experimental rhabdomyolysis. Crit Care Med. 2005;33:2579-86.

143. 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.

144. Homsi E, Barreiro M, Orlando J, Higa E. Prophylaxis of acute renal failure in patients with rhabdomyolysis. Ren Fail. 1997;19:283-8.

145. Brown C, Rhee P, Chan L, et al. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? J Trauma. 2004;56:1191-6.