

Review

Rhabdomyolysis: Review of the literature

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Abstract

Rhabdomyolysis is a serious and potentially life threatening condition. Although consensus criteria for rhabdomyolysis is lacking, a reasonable definition is elevation of serum creatine kinase activity of at least 10 times the upper limit of normal followed by a rapid decrease of the sCK level to (near) normal values. The clinical presentation can vary widely, classical features are myalgia, weakness and pigmenturia. However, this classic triad is seen in less than 10% of patients. Acute renal failure due to acute tubular necrosis as a result of mechanical obstruction by myoglobin is the most common complication, in particular if sCK is >16,000 IU/l, which may be as high as 100,000 IU/l. Mortality rate is approximately 10% and significantly higher in patients with acute renal failure. Timely recognition of rhabdomyolysis is key for treatment. In the acute phase, treatment should be aimed at preserving renal function, resolving compartment syndrome, restoring metabolic derangements, and volume replacement. Most patients experience only one episode of rhabdomyolysis, mostly by substance abuse, medication, trauma or epileptic seizures. In case of recurrent rhabdomyolysis, a history of exercise intolerance or a positive family history for neuromuscular disorders, further investigations are needed to identify the underlying, often genetic, disorder. We propose a diagnostic algorithm for use in clinical practice.

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1. Introduction

Rhabdomyolysis was first reported in Germany in 1881 [1] and described in more detail after the Battle of London, during the Second World War [2]. Rhabdomyolysis results from the rapid breakdown of skeletal muscle fibres, which leads to leakage of potentially toxic cellular contents into the systemic circulation [3,4]. The syndrome is characterised by elevation of serum creatine kinase (sCK) activity to at least 10 times the upper limit of normal

followed by a fast decrease. There is no consensus on the definition of rhabdomyolysis. Some adhere to the afore-mentioned increase whereas others consider a smaller increase in sCK elevation (>5 times) sufficient for a diagnosis of rhabdomyolysis [3,5]. The American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute Clinical Advisory on the use and safety of statins defined statin-induced rhabdomyolysis as a sCK elevation greater than 10 times the upper limit of normal [6,7]. In most patients, sCK is normal between acute episodes of rhabdomyolysis except, for patients with muscular dystrophies, myositis or a defect in glycogen metabolism. Rhabdomyolysis may be accompanied by myoglobinuria, due to an excessive amount of myoglobin in urine,

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presenting as dark tea or cola-coloured urine [8]. In this review, we summarise the existing literature regarding the pathophysiology, clinical presentation, aetiology, diagnosis, and management of rhabdomyolysis. Literature has been collected by a search of PubMed using the terms rhabdomyolysis, myoglobinuria, creatine kinase, hyper-CK-emia, myoglobin, transient creatine phosphokinase elevation, and metabolic myopathy.

2. Epidemiology

Knowledge about the actual frequency of rhabdomyolysis is limited. There is no prospective study on incidence of rhabdomyolysis and many mild cases of rhabdomyolysis probably go unrecognised. Approximately 26,000 cases of rhabdomyolysis are reported annually in the United States [3,9]. In 0.074% of patients admitted to a large university hospital over a 7-year period a CK serum activity of more than 5000 IU/l was found [10]. A study among military trainees over a period of 6 years found an incidence of exertional rhabdomyolysis of 22.2 cases per 100,000 trainees per year [11]. An incidence of four cases of rhabdomyolysis per 1500 patient consultations has been reported in a paediatric study [12]. Rhabdomyolysis also occurs in animals. For example, about 3% of exercising horses experience rhabdomyolysis. These horses have similar signs and underlying aetiologies as in humans [13].

Little is known about the recurrence rate of rhabdomyolysis. A study of 475 patients found relapses in 11%, whereas the above-mentioned study among military trainees showed a recurrence risk of 0.08% per person per year [11]. In a retrospective study in children with rhabdomyolysis five percent of patients exhibited a recurrence during 6 years of follow up [14]. Mackay et al. [15] reported a similar recurrence rate in children (8%).

3. Pathophysiology

Irrespective of the cause of rhabdomyolysis, the pathophysiologic events follow a common pathway. Normally, ion pumps and channels in the sarcolemma maintain a low intracellular Na^+ and Ca^{2+} and a high intracellular K^+ concentration [16]. Direct injury to the sarcolemma or failure of energy production can cause rhabdomyolysis. Shortage of energy results in pump dysfunction (Na/K -ATPase, Ca^{2+} ATPase pump), which leads to increased cellular permeability to sodium ions and consequently increased intracellular calcium concentration [3,17]. High intracellular calcium levels enhance the activation of calcium-dependent proteases and phospholipases, which contributes to destruction of myofibrillar, cytoskeletal and membrane proteins. Subsequently, large quantities of intracellular metabolites (potassium, phosphate and urate) as well as intracellular proteins (aldolase, myoglobin, creatine kinase, lactate dehydrogenase, aspartate transaminase) leak into the circulation [3,18,19]. Myoglobin is a haem protein,

functioning as an oxygen carrier in skeletal muscle. Normally myoglobin is bound to plasma globulins. In case of rhabdomyolysis myoglobin levels can exceed the protein-binding capacity of the plasma, and myoglobin precipitates in the glomerular filtrate. The mechanical obstruction of tubules by myoglobin is an important factor causing acute renal failure (ARF). Other contributing factors of ARF are vasoconstriction, hypovolemia, and direct renal toxic effect of myoglobin [20–23].

4. Symptoms and signs

The presentation of rhabdomyolysis varies widely between patients and ranges from asymptomatic sCK elevation to a life-threatening condition with electrolyte disturbance, cardiac arrhythmia, ARF and disseminated intravascular coagulation (DIC).

Classical clinical features are (sub)acute-onset myalgia, transient muscle weakness and pigmenturia (dark tea or cola-coloured urine), caused by an excessive amount of myoglobin (>1.5 – 3.0 mg/l) in the urine [3,17–19,24–26]. However, this triad is observed in less than 10% of the patients [21]. At the onset of an episode of rhabdomyolysis clinical symptoms may be indefinable or absent in up to 50% [19]. Many symptoms are non-specific, including myalgia, swelling, and weakness. Patients may have systemic features like fever, nausea, emesis, confusion, agitation, delirium and anuria. Muscle weakness can occur in any body part, but most frequently proximal leg muscles are affected. Organ failure can occur, depending upon the extent and severity of muscle damage and is the cause of death in about 8% of cases [21,25]. Severe hyperkalemia can cause cardiac arrhythmia and lead to cardiac arrest. The release of large amounts of phosphate leads to hypocalcaemia, which can also result in cardiac arrhythmia. The most important complication is acute renal failure, occurring in 14–46% due to acute tubular necrosis as a result of obstruction by myoglobin [3,21,27,28]. In two small studies on children a risk of 42% and 50% was found, respectively [29,30]. A larger study of Mannix et al. [31] reported an incidence of ARF of 5%. Serum CK activities higher than 16,000 U/L are more likely to be associated with renal failure [10,21,27]. In one study, quantification of the risk of ARF was estimated to be 35% when sCK was 5,000–15,000 IU/l and about 70% if sCK was $>15,000$ IU/l [10]. Hepatic dysfunction occurs in 25% of patients with rhabdomyolysis. The pathogenesis is probably multifactorial. An important factor is hepatic inflammation, which is triggered by proteases released from injured muscle [3,5,32]. Compartmental syndrome in the extremities does not seem to be rare in rhabdomyolysis, albeit that data on its incidence is lacking. The impairment of muscle cells during rhabdomyolysis and the massive influx of calcium and sodium induce the accumulation of large amounts of extracellular fluid into the cells, resulting in the formation of local oedema and an

increase in intramuscular pressure. Is it believed that components released from the damaged muscles may activate the coagulation pathway which in turn may lead to disseminated intravascular coagulation (DIC) in some [24] (Table 1).

5. Diagnosis

5.1. Laboratory tests

The diagnosis of rhabdomyolysis is based on a more than 10 times elevated sCK. The degree of sCK elevation is proportional to the muscle injury. Approximately 2–12 h after the onset of muscle injury sCK increases. A peak concentration occurs at 24–72 h and then sCK declines to baseline values in the course of 3–5 days [17,18,24,25,33]. CK has a significant longer half-life (1.5 days) in comparison with myoglobin (2–4 h) [25]. The rapid renal clearance of myoglobin results in a low plasma level. After muscle damage the circulating myoglobin levels exceed the plasma protein binding capacity. Unbound myoglobin is filtered by the glomeruli and is then excreted in the urine. Visible myoglobinuria occurs if the level of myoglobin in the urine exceeds 100 mg/dl [19,33,34]. Thus, myoglobinuria easily escapes attention. Other laboratory investigations include complete blood count, bilirubin, uric acid, kidney function, liver function, serum electrolytes (especially potassium), and an arterial blood gas to analyse acid–base balance [3,24,33,35].

5.2. Electrocardiogram (ECG)

When electrolyte disturbances are present (e.g. hyperkalemia) an ECG should be performed to rule out cardiac arrhythmias [24].

6. Differential diagnosis

The differential diagnosis of hyperCKemia (serum CK activity more than 10 times the upper limit of normal) is extensive and includes myositis, muscular dystrophies, and endocrine disorders such as hyperthyroidism or hypothyroidism. Patients with subacute onset myositis may also suffer from myalgia. In contrast with acute onset in rhabdomyolysis, symptoms and signs in myositis develop over a period of weeks. In rhabdomyolysis serum CK activity returns to normal in days to weeks, whereas

in myositis sCK remains highly elevated until treatment is initiated. Muscle biopsy can be helpful to distinguish between the two conditions.

The hereditary muscular dystrophies are characterised by progressive muscle weakness, developing over years. Detailed history including family history is needed. DNA analysis and immunohistochemical and histochemical analysis of muscle tissue can be helpful to find the underlying genetic defect.

Haematuria may result in reddish brown urine. To distinguish this condition from myoglobinuria, urine must be checked on red blood cells. Also various foods and drugs can be the cause of red/brown urine. However, these patients as well as those with haematuria, have normal serum CK activity.

7. Causes

Many causes of rhabdomyolysis have been identified (Table 2). They can be categorised into acquired and inherited causes. In 75% of patients a first episode of rhabdomyolysis is provoked by an acquired cause [36]. The most common acquired causes are: substance abuse (34%), medication (11%), trauma (9%) and epileptic seizures (7%) [28]. Less frequent causes include metabolic disturbance, infections, local muscle ischaemia [37–39], generalised muscle ischemia [24], prolonged immobilisation [24,40], exercise, and excessive heat [24]. In 60% of patients there are two or more causative factors [19,24,25,28,41–43]. The main causes for rhabdomyolysis in children are viral myositis (38%), trauma (26%), dermatomyositis (5%), drug overdose (4%), exercise (4%), and metabolic disorders (e.g., hypokalaemia, diabetic ketoacidosis) (4%) [14,16,31,44]. Suspicion of an inherited underlying cause should arise when rhabdomyolysis re-occurs [41,45–52], or in case of a positive family history, concomitant presence of exercise intolerance, recurrent muscle cramps. One must be aware that some of the above mentioned acquired causes i.e., infections, exercise or use of medication, can be a trigger of rhabdomyolysis in patients with an underlying inherited metabolic disorder.

Inherited metabolic myopathies include inborn errors in glycogenolysis or terminal glycolysis [45,53], the pathway of short-, medium- or long-chain fatty acid oxidation [40,45,54], the triacylglycerol (TAG) synthesis pathway [55], the purine nucleotide cycle [46], and the mitochondrial oxidative phosphorylation system including the respiratory chain [45]. Of these, the subgroup of short-chain fatty acid oxidation deficiencies (SCAD) is a complex group, in which a genotype to phenotype relation is lacking. There are SCAD patients with typical clinical characteristics, but also SCAD relatives of SCAD patients free of any symptoms [56]. Episodes of rhabdomyolysis can also occur in patients with muscular dystrophies [57]. Another condition associated with rhabdomyolysis is malignant hyperthermia. Malignant hyperthermia is characterized by a hypermetabolic state

Table 1
Complications of rhabdomyolysis [24].

Acute renal failure
Hyperkalemia
Hypocalcaemia
Hepatic inflammation
Cardiac arrhythmia and cardiac arrest
Disseminated intravascular coagulation
Compartment syndrome

Table 2
Causes of rhabdomyolysis.

Acquired [16–18,24,40]

Non Traumatic

Non Exertional Causes

- Alcohol/drug abuse
ethanol, methanol, ethylene glycol, heroin, methadone, barbiturates, cocaine, caffeine, amphetamine, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), phencyclidine, benzodiazepines, toluene (from glue sniffing), gasoline/paint sniffing
- Medication
salicylates, fibric acid derivatives (bezafibrate, clofibrate, fenofibrate, gemfibrozil), neuroleptics, antipsychotics (haloperidol, fluphenazine, perphenazine, chlorpromazine), quinine, corticosteroids, statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, cerivastatin), theophylline, cyclic antidepressants, selective serotonin reuptake inhibitors, antibiotics (fluroquinolones, pyrazinamide, trimethoprim/ sulphonamide, amphotericin B, itraconazole, levofloxacin), zidovudine, benzodiazepines, antihistamines, aminocaproic acid, phenylpropanolamine
- Toxic agents
carbon monoxide (CO), hemlock herbs from quail, snake bites, spider venom, massive honey bee envenomations, Tricholoma Equestre (mushroom), buffalo fish
- Anesthetics and neuromuscular blocking agents
barbiturates, benzodiazepines, propofol, succinylcholine in patients with Duchenne/Becker muscular dystrophy
- Infections
viral: influenza A and B, human immunodeficiency virus, enterovirus, adenovirus, Coxsackie virus, Epstein-Barr virus, echovirus, cytomegalovirus, herpes simplex virus, varicella-zoster virus, West Nile virus. Bacterial: Legionella species, Salmonella species, Francisella species, Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus, Pseudomonas aeruginosa, Neisseria meningitidis, Haemophilus influenza, Coxiella burnetii, Leptospira species, Mycoplasma species, Escherichia coli. Fungal and malaria infections
- Electrolyte disturbances
hyponatraemia, hypernatraemia, hypokalaemia, hypophosphataemia, hypocalcaemia, hyperosmotic conditions
- Endocrine disorders
hypothyroidism, hyperthyroidism, diabetic ketoacidosis, non-ketotic hyperosmolar diabetic coma, hyperaldosteronism
- Idiopathic inflammatory myopathies
polymyositis, dermatomyositis
- Temperature extremes
Heatstroke, malignant hyperthermia, exposure to cold
- Muscle ischaemia
thrombosis, embolism
- Neuroleptic malignant syndrome

Exertional Causes

- Extreme physical exertion
- Sickle cell disease (crisis)
- Status epilepticus
- Hyperkinetic syndrome
Severe dystonia
- Status asthmaticus

Traumatic

- Multiple injury
 - Crush injury
bombings, earthquakes, building collapse, mine accidents, train or motor vehicle accidents
 - High-voltage electrical injury
 - Extensive third-degree burns
 - Vascular/orthopaedic surgery
Intra-operative use of tourniquets, tight dressings or casts, prolonged application of air splints or pneumatic anti-shock garments and clamping of vessels during surgery
 - Prolonged immobility
Immobilisation after trauma, anaesthesia, coma, drug or alcohol-induced unconsciousness
-

Genetic [3,24,40,46–48,45,53,57]

- Terminal glycolysis/Glycogenolysis
Myophosphorylase, phosphoglycerate mutase, phosphofructokinase, phosphorylase b kinase, lactate dehydrogenase, phosphoglycerate kinase, and debrancher enzyme deficiency
- Lipid metabolism
Carnitine palmitoyltransferase (CPT II), carnitine, short- /medium- /very long-chain acyl-CoA dehydrogenase (SCAD, MCAD, VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), electron transfer flavoprotein (ETF)- and ETF dehydrogenase, long-chain 3-ketothiolase, trifunctional enzyme deficiency
- Krebs cycle
Aconitase, lipoamide dehydrogenase deficiency
- Purine Nucleotide Cycle
Adenylosuccinate synthetase, adenylosuccinate lyase, adenosine triphosphatase deficiency
- Mitochondrial respiratory chain

Table 2 (continued)

Genetic [3,24,40,46–48,45,53,57] (continued)

Mitochondrial tRNA point mutations, complex I deficiency, succinate dehydrogenase (complex II), complex III, coenzyme Q10, cytochrome-c-oxidase deficiency
- Myopathies
Muscular dystrophies (Duchenne, Becker, Emery-Dreifuss, Miyoshi myopathy (dysferlinopathy), fukutin-related proteinopathy (LGMD2I), anoctaminopathy (LGMD2L, Miyoshi-type distal muscular dystrophy), malignant hyperthermia due to ryanodine receptor type I (RYR1) mutations
Other
Methyl-acyl-CoA-racemase (AMACR) deficiency, Lipin-1 (LPIN1) mutation

with elevation of end-tidal carbon dioxide (ETCO₂) concentration, muscle rigidity, tachycardia, metabolic acidosis, and rapid increase in body temperature as a response to certain anaesthetic agents [58,59]. All inhalation anaesthetics (except nitrous oxide) and the muscle relaxant succinylcholine are triggers for malignant hyperthermia [58]. In most cases, the syndrome is caused by a defect in the ryanodine receptor due to mutations in the RYR-1 gene located on chromosome 19q13.1 [58]. Heat and exercise induced rhabdomyolysis can also be manifestations of RYR-1 mutation [60,61]. Rhabdomyolysis is also described in patients with an α -Methyl-acyl-CoA-racemase (AMACR) deficiency, a rare peroxisomal disorder, leading to the accumulation of (2R)-pristanic acid and the bile acid synthesis intermediates di- and trihydroxycholestanoic acid [62]. Stroke-like episodes, demyelinating neuropathy, relapsing encephalopathy, seizures and cognitive decline are more prominent features of this disease. Mutations in the Lipin-1 (LPIN1) gene are found to be a cause of recurrent rhabdomyolysis in children. This gene encodes the muscle-specific phosphatidic acid phosphatase, a key enzyme in triglyceride and membrane phospholipid biosynthesis [55,57,63–65]. The episodes of rhabdomyolysis are mostly triggered by fever and intercurrent infections, and to a lesser extent by fasting or exercise [63,64]. The prognosis of LPIN1 deficiency is poor, with up to one-third of patients dying during an episode of rhabdomyolysis [64]. In about 60% of patients with recurrent rhabdomyolysis no identifiable cause can be found. These cases are termed idiopathic or Meyer–Betz syndrome [19,24].

8. Investigations to identify rhabdomyolysis and the underlying cause

The first step in practice is taking a detailed history asking for symptoms of rhabdomyolysis, like (sub)acute-onset myalgia, transient muscle weakness and pigmenturia. When the history is compatible with rhabdomyolysis it is important to ask about provoking factors including infection, fasting, intensity and duration of exercise, temperature, general anaesthesia, the use of medication, alcohol or drug abuse and the exposition to toxic agents. In addition second-wind or out-of-wind phenomenon should be questioned. Patients with disorders in glyco(geno)lysis are described to have an intolerance of brief exercise with great intensity, such as

sprinting or lifting heavy loads, or by less intense but sustained dynamic exercise. Patients with McArdle's disease can experience a second-wind phenomenon; improvement in exercise tolerance after a short break when developing muscle complaints during strenuous activity, because of increase of circulating glucose due to mobilisation of hepatic glucose [45,66–68]. Patients with phosphofructokinase deficiency can experience an out-of-wind phenomenon; exacerbation of exercise intolerance after administration of glucose, because of a reduction in the availability of free fatty acids and ketones [45]. In patients with a disorder of the fatty acid oxidation the ability to perform short-duration, intense exercise is not impaired because glycogen is the primary substrate used for energy production the first 10–30 min. These patients develop symptoms after prolonged low-intensity exercise (usually more than 30 min) or during fasting, when fatty acids are used as fuel [45].

The second step is to confirm the diagnosis of rhabdomyolysis by neurological examination, measurement of sCK and/or myoglobinuria. The third step is to reveal the underlying cause of rhabdomyolysis. A diagnostic algorithm was developed based on expert opinion and literature data (Fig. 1) [36]. If a patient experienced a first episode of rhabdomyolysis and (family) history is non-contributory, an environmental factor is the most likely cause and in about 75% of patients, the etiology is acquired. In such cases, the chance of relapse is very low and no further investigation is needed [19,28].

If an underlying metabolic myopathy is suspected, we recommend the sequence of investigations shown in the flow chart (Fig. 1). Blood tests should screen for endocrine disorders and electrolyte disturbances. Clues to certain glycogenoses include presence of haemolytic anaemia (phosphofructokinase deficiency or phosphoglycerate kinase deficiency) or hyperuricemia (phosphofructokinase deficiency or myophosphorylase deficiency) [69–72]. A non-ischemic forearm exercise test [73] and a fasting blood test for acylcarnitine profile can guide further investigation. In a patient with an abnormal acylcarnitine profile, the next step is enzymatic studies in lymphocytes or cultured skin fibroblasts followed by DNA analysis (see Wanders et al. [74] for review).

Paediatricians could consider screening for LPIN1 mutations at early stage of the metabolic work up, particularly in children who develop rhabdomyolysis in the setting of febrile infections [64].

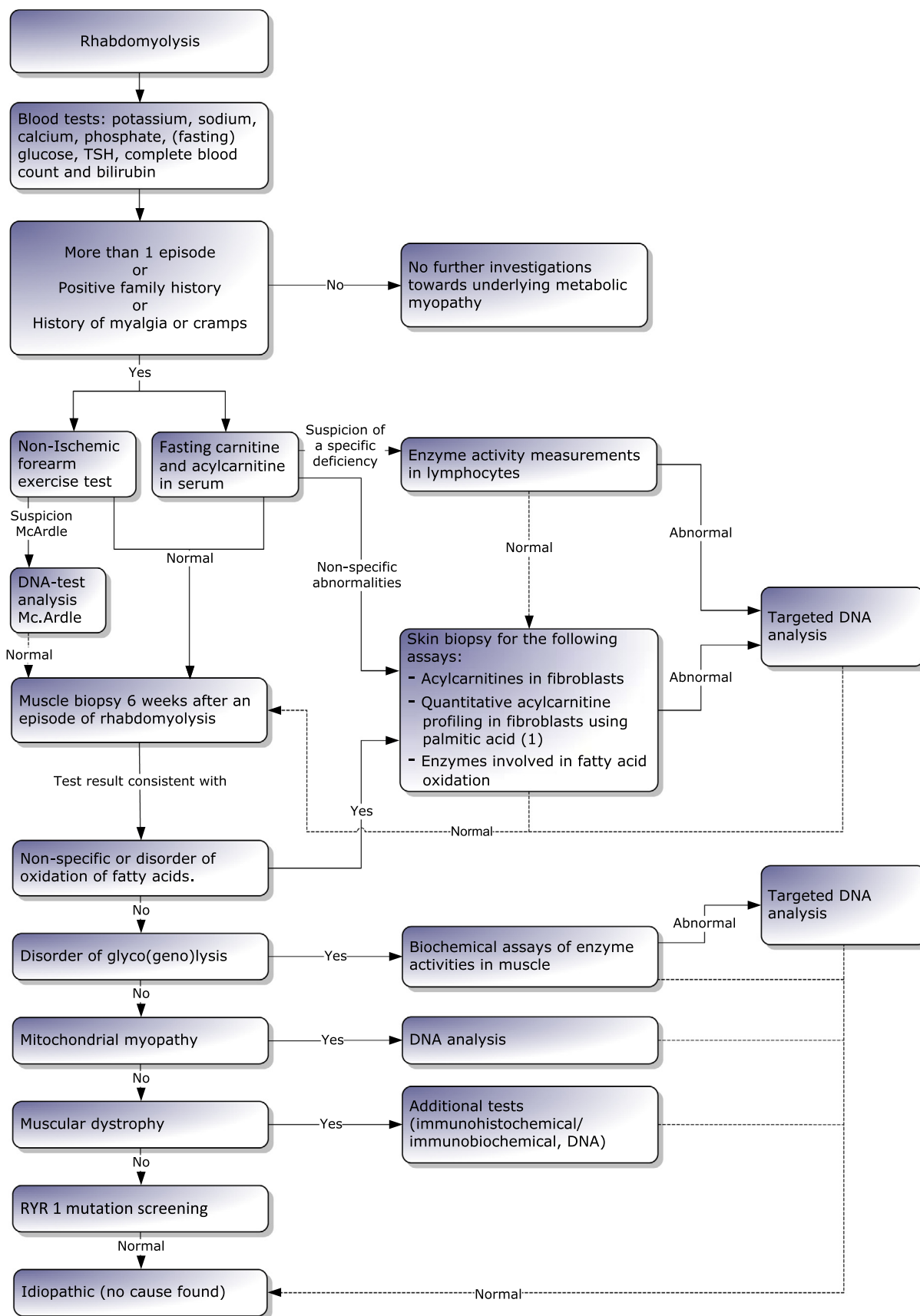


Fig. 1. Clinical approach in patients with rhabdomyolysis. 1. A method for the investigation of mitochondrial fatty acid beta-oxidation in cultured fibroblasts. Monolayer cultures are incubated with palmitic acid and L-carnitine and the acylcarnitines produced by the cells are extracted from the cell suspension and analysed.

In case these test(s) reveal(s) no abnormalities the next step is a muscle biopsy. The recommended timing of the muscle biopsy, preferably a few weeks after an episode of rhabdomyolysis, is important, because if the biopsy is taken too early, necrotic changes of the muscle fibres may disguise the underlying defect [40,57,75].

If, following the flow chart, an underlying defect ascribed to a specific enzyme deficiency is suspected, targeted DNA analysis should be performed. RYR 1 mutation screening can be performed for confirmation or exclusion of malignant hyperthermia. These last steps of the protocol are time-consuming investigations, which should be performed in highly specialised laboratories only. In the future this may change because DNA analysis becomes more readily available and affordable.

9. Management

In the acute phase treatment should be aimed at preserving renal function and restoring metabolic derangements. Early and adequate volume replacement with NaCl 0.9% (no potassium or lactate containing solutions!) is of utmost importance in preventing acute renal failure [25,76–78]. Volume expansion increases renal blood flow and, consequently, glomerular filtration and urination. The infusion should begin at a rate of 1.5 L/h to maintain a urine output of 200–300 ml/h. Intravenous fluid should be continued until sCK activity in plasma has declined preferably to 1000 IU/l or below. Careful monitoring is essential, because the massive fluid infusion can lead to congestive heart failure and pulmonary edema, particularly in older patients or patients with cardiopulmonary risk factors [5,25,22]. Severe electrolyte and metabolic abnormalities must be corrected. Haemodialysis should be considered when life-threatening hyperkalemia and metabolic acidosis occur.

Although not proven by randomised control trials, some experts recommend the addition of mannitol and bicarbonate. Alkalinization of the urine (target pH 6.5) promotes myoglobin washout. Bicarbonate also corrects the metabolic acidosis and, subsequently, hyperkalemia [21,25,79,80]. Mannitol leads to an increase in blood flow and glomerular filtration, which reduces the obstruction by myoglobin casts [76]. Mannitol must be given after volume replacement and must be avoided in patients with oliguria [24]. Early hypocalcaemia should not be treated unless severe hyperkalemia is present. A few case reports show effectiveness of corticosteroids in the treatment of rhabdomyolysis, but this is not considered standard practice [34,81–83]. Compartment syndrome requires orthopaedic consultation. If the compartment pressure exceeds 50 mmHg, or if pressure persists between 30 and 50 mmHg for longer than 6 h decompressive fasciotomy must be considered [25,35,84]. Haemorrhagic complications in patients with DIC and rhabdomyolysis require careful management.

Subsequently, the underlying cause of the episode of rhabdomyolysis should be identified and – if possible – treated. Drugs and toxins should be eliminated and detoxified (e.g., haemodialysis/antidotes) when possible [24]. If a metabolic myopathy or muscular dystrophy is identified, the risk of new episodes of rhabdomyolysis must be minimised. Intense exercise should be avoided in patients with a disorder of the glyco(geno)lysis and prolonged exercise or fasting should be avoided in patients with a disorder of the fatty acid oxidation. Depending on the underlying defect dietary measures can be taken. For example a high carbohydrates and low triglycerides diet in patients with a disorder of the fatty acid oxidation disorders, [44,85] or a dietary restriction of phytanic acid [62]. In patients with CPT2 deficiency, preventive measures include taking frequent meals with carbohydrate intake before and during prolonged exercise [86]. In patients with Duchenne muscular dystrophy or Becker dystrophy exposure to Succinylcholine should be avoided during anaesthesia [87]. Also in patients with malignant hyperthermia one should be cautious using anaesthetics. It is important to instruct patients about provoking triggers for rhabdomyolysis and when to seek professional advice. Bezafibrate was described as a potential pharmacologic treatment in patients with a mild form of CPT2 deficiency by stimulating the expression of the mutated gene, a recent trial however showed it was not effective [88–91].

10. Prognosis

The prognosis of rhabdomyolysis depends on the complications resulting from the rhabdomyolysis and the underlying cause. When treated early and aggressively, an episode of rhabdomyolysis has an excellent prognosis [18,24,33,35,92]. The mortality rate from rhabdomyolysis is about 8–10% [19,25,33]. Prognosis is substantially worse if ARF develops [10,27]. A Dutch study found 17% mortality in patients without ARF and 51% in those with ARF ($P < 0.01$, $N = 93$, with sCK > 5000 U/L). Ward [27] described a mortality rate of 8% in the group without ARF and 42% in the ARF group. The mortality rate in children is about 7–10%, but all children died due to the underlying aetiology of rhabdomyolysis, such as trauma, burns and sepsis, and not because of complications of rhabdomyolysis [14,31].

References

- [1] Fleischer R. Ueber eine neue Form von Haemoglobinurie beim Menschen. *Berl Klin Wochenschr* 1881;18:691.
- [2] Bywaters EG, Beall D. Crush injuries with impairment of renal function. 1941. *J Am Soc Nephrol* 1998;9(2):322–32.
- [3] Sauret JM, Marinides G, Wang GK. Rhabdomyolysis. *Am Fam Physician* 2002;65(5):907–12.
- [4] Adams EC. Differentiation of myoglobin and hemoglobin in biological fluids. *Ann Clin Lab Sci* 1980;10(6):493–9.

- [5] Lane R, Phillips M. Rhabdomyolysis. *BMJ* 2003;327(7407):115–6.
- [6] Antons KA, Williams CD, Baker SK, Phillips PS. Clinical perspectives of statin-induced rhabdomyolysis. *Am J Med* 2006;119(5):400–9.
- [7] Pasternak RC, Smith Jr SC, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Stroke* 2002;33(9):2337–41.
- [8] Russell TA. Acute renal failure related to rhabdomyolysis: pathophysiology, diagnosis, and collaborative management. *Nephrol Nurs J* 2000;27(6):567–75, quiz 576–7.
- [9] Brown CV, 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(6):1191–6.
- [10] Veenstra J, Smit WM, Krediet RT, Arisz L. Relationship between elevated creatine phosphokinase and the clinical spectrum of rhabdomyolysis. *Nephrol Dial Transpl* 1994;9(6):637–41.
- [11] Alpers JP, Jones Jr LK. Natural history of exertional rhabdomyolysis: a population-based analysis. *Muscle Nerve* 2010;42(4):487–91.
- [12] Chamberlain MC. Rhabdomyolysis in children: a 3-year retrospective study. *Pediatr Neurol* 1991;7(3):226–8.
- [13] Valberg SJ. The management of tying-up in sport horses: challenges and successes. *Feed Vet Manage Sport Horse* 2010:81–93.
- [14] Perreault S, Birca A, Piper D, Nadeau A, Gauvin F, Vanasse M. Transient creatine phosphokinase elevations in children: a single-center experience. *J Pediatr* 2011;159(4):682–5.
- [15] Mackay MT, Kornberg AJ, Shield LK, Dennett X. Benign acute childhood myositis: laboratory and clinical features. *Neurology* 1999;53(9):2127–31.
- [16] Luck RP, Verbin S. Rhabdomyolysis: a review of clinical presentation, etiology, diagnosis, and management. *Pediatr Emerg Care* 2008;24(4):262–8.
- [17] Shapiro ML, Baldea A, Luchette FA. Rhabdomyolysis in the intensive care unit. *J Intensive Care Med* 2012;27(6):335–42.
- [18] Huerta-Alardin AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis – an overview for clinicians. *Crit Care* 2005;9(2):158–69.
- [19] Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine (Baltimore)* 1982;61(3):141–52.
- [20] Al-Ismaili Z, Piccioni M, Zappitelli M. Rhabdomyolysis: pathogenesis of renal injury and management. *Pediatr Nephrol* 2011;26(10):1781–8.
- [21] Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med* 2009;361(1):62–72.
- [22] Holt SG, Moore KP. Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. *Intensive Care Med* 2001;27(5):803–11.
- [23] Holt S, Moore K. Pathogenesis of renal failure in rhabdomyolysis: the role of myoglobin. *Exp Nephrol* 2000;8(2):72–6.
- [24] Khan FY. Rhabdomyolysis: a review of the literature. *Neth J Med* 2009;67(9):272–83.
- [25] Cervellin G, Comelli I, Lippi G. Rhabdomyolysis: historical background, clinical, diagnostic and therapeutic features. *Clin Chem Lab Med* 2010;48(6):749–56.
- [26] Chatzizisis YS, Misirli G, Hatzitolios AI, Giannoglou GD. The syndrome of rhabdomyolysis: complications and treatment. *Eur J Intern Med* 2008;19(8):568–74.
- [27] Ward MM. Factors predictive of acute renal failure in rhabdomyolysis. *Arch Intern Med* 1988;148(7):1553–7.
- [28] Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine (Baltimore)* 2005;84(6):377–85.
- [29] Watemberg N, Leshner RL, Armstrong BA, Lerman-Sagie T. Acute pediatric rhabdomyolysis. *J Child Neurol* 2000;15(4):222–7.
- [30] Watanabe T. Rhabdomyolysis and acute renal failure in children. *Pediatr Nephrol* 2001;16(12):1072–5.
- [31] Mannix R, Tan ML, Wright R, Baskin M. Acute pediatric rhabdomyolysis: causes and rates of renal failure. *Pediatrics* 2006;118(5):2119–25.
- [32] Akmal M, Massry SG. Reversible hepatic dysfunction associated with rhabdomyolysis. *Am J Nephrol* 1990;10(1):49–52.
- [33] Bagley WH, Yang H, Shah KH. Rhabdomyolysis. *Intern Emerg Med* 2007;2(3):210–8.
- [34] Brown J, Mitchell S. A complicated case of exertional heat stroke in a military setting with persistent elevation of creatine phosphokinase. *Mil Med* 1992;157(2):101–3.
- [35] Vanholder R, Sever MS, Ereke E, Lameire N. Rhabdomyolysis. *J Am Soc Nephrol* 2000;11(8):1553–61.
- [36] Zutt R, van der Kooij AJ, Linthorst GE, Wanders RJ, Verschuuren JJ, de Visser M. Recurrent rhabdomyolysis: screening for underlying disease. *Ned Tijdschr Geneesk* 2010;154:A2290.
- [37] Williams Jr JE, Tucker DB, Read 3rd JM. Rhabdomyolysis-myoglobinuria: consequences of prolonged tourniquet. *J Foot Surg* 1983;22(1):52–6.
- [38] Taylor DC, Salvian AJ, Shackleton CR. Crush syndrome complicating pneumatic antishock garment (PASG) use. *Injury* 1988;19(1):43–4.
- [39] Slater MS, Mullins RJ. Rhabdomyolysis and myoglobinuric renal failure in trauma and surgical patients: a review. *J Am Coll Surg* 1998;186(6):693–716.
- [40] Warren JD, Blumberg PC, Thompson PD. Rhabdomyolysis: a review. *Muscle Nerve* 2002;25(3):332–47.
- [41] Allison RC, Bedsole DL. The other medical causes of rhabdomyolysis. *Am J Med Sci* 2003;326(2):79–88.
- [42] Boucree MC. Legionnaire's disease and acute renal failure: a case report and literature review. *J Natl Med Assoc* 1988;80(10):1065–71.
- [43] Efstratiadis G, Voulgaridou A, Nikiforou D, Kyventidis A, Kourkouni E, Vergoulas G. Rhabdomyolysis updated. *Hippokratia* 2007;11(3):129–37.
- [44] Elsayed EF, Reilly RF. Rhabdomyolysis: a review, with emphasis on the pediatric population. *Pediatr Nephrol* 2010;25(1):7–18.
- [45] Berardo A, DiMauro S, Hirano M. A diagnostic algorithm for metabolic myopathies. *Curr Neurol Neurosci Rep* 2010;10(2):118–26.
- [46] Darras BT, Friedman NR. Metabolic myopathies: a clinical approach; part I. *Pediatr Neurol* 2000;22(2):87–97.
- [47] Darras BT, Friedman NR. Metabolic myopathies: a clinical approach; part II. *Pediatr Neurol* 2000;22(3):171–81.
- [48] Cornelio F, Di Donato S. Myopathies due to enzyme deficiencies. *J Neurol* 1985;232(6):329–40.
- [49] Patten BM, Wood JM, Harati Y, Hefferan P, Howell RR. Familial recurrent rhabdomyolysis due to carnitine palmitoyl transferase deficiency. *Am J Med* 1979;67(1):167–71.
- [50] Poels PJ, Wevers RA, Braakhekke JP, Benders AA, Veerkamp JH, Joosten EM. Exertional rhabdomyolysis in a patient with calcium adenosine triphosphatase deficiency. *J Neurol Neurosurg Psychiatry* 1993;56(7):823–6.
- [51] Tonin P, Lewis P, Servidei S, DiMauro S. Metabolic causes of myoglobinuria. *Ann Neurol* 1990;27(2):181–5.
- [52] Singh D, Chander V, Chopra K. Rhabdomyolysis. *Methods Find Exp Clin Pharmacol* 2005;27(1):39–48.
- [53] DiMauro S, Garone C, Naini A. Metabolic myopathies. *Curr Rheumatol Rep* 2010;12(5):386–93.
- [54] Gregersen N, Bross P, Andresen BS. Genetic defects in fatty acid beta-oxidation and acyl-CoA dehydrogenases. molecular pathogenesis and genotype-phenotype relationships. *Eur J Biochem* 2004;271(3):470–82.
- [55] Zeharia A, Shaag A, Houtkooper RH, et al. Mutations in LPIN1 cause recurrent acute myoglobinuria in childhood. *Am J Hum Genet* 2008;83(4):489–94.
- [56] van Maldegem BT, Duran M, Wanders RJ, et al. Clinical, biochemical, and genetic heterogeneity in short-chain acyl-coenzyme A dehydrogenase deficiency. *JAMA* 2006;296(8):943–52.
- [57] Quinlivan R, Jungbluth H. Myopathic causes of exercise intolerance with rhabdomyolysis. *Dev Med Child Neurol* 2012;54(10):886–91.
- [58] Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. *Orphanet J Rare Dis* 2007;24(2):21.

- [59] Hopkins PM. Malignant hyperthermia: advances in clinical management and diagnosis. *Br J Anaesth* 2000;85(1):118–28.
- [60] Denborough M. Malignant hyperthermia. *Lancet* 1998;352(9134):1131–6.
- [61] Dlamini N, Voermans NC, Lillis S, et al. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. *Neuromuscul Disord* 2013;23(7):540–8.
- [62] Kapina V, Sedel F, Truffert A, et al. Relapsing rhabdomyolysis due to peroxisomal alpha-methylacyl-coa racemase deficiency. *Neurology* 2010;75(14):1300–2.
- [63] Michot C, Hubert L, Romero NB, et al. Study of LPIN1, LPIN2 and LPIN3 in rhabdomyolysis and exercise-induced myalgia. *J Inherit Metab Dis* 2012;35(6):1119–28.
- [64] Michot C, Hubert L, Brivet M, et al. LPIN1 gene mutations: a major cause of severe rhabdomyolysis in early childhood. *Hum Mutat* 2010;31(7):E1564–73.
- [65] Bergounioux J, Brassier A, Rambaud C, et al. Fatal rhabdomyolysis in 2 children with LPIN1 mutations. *J Pediatr* 2012;160(6):1052–4.
- [66] Lucia A, Nogales-Gadea G, Perez M, Martin MA, Andreu AL, Arenas J. McArdle disease: what do neurologists need to know? *Nat Clin Pract Neurol* 2008;4(10):568–77.
- [67] Vissing J, Haller RG. Mechanisms of exertional fatigue in muscle glycogenoses. *Neuromuscul Disord* 2012;22(Suppl 3):S168–71.
- [68] Vissing J, Haller RG. A diagnostic cycle test for McArdle's disease. *Ann Neurol* 2003;54(4):539–42.
- [69] Fujii H, Miwa S. Other erythrocyte enzyme deficiencies associated with non-haematological symptoms: phosphoglycerate kinase and phosphofructokinase deficiency. *Baillieres Best Pract Res Clin Haematol* 2000;13(1):141–8.
- [70] Toscano A, Musumeci O. Tarui disease and distal glycogenoses: clinical and genetic update. *Acta Myol* 2007;26(2):105–7.
- [71] Beutler E. PGK deficiency. *Br J Haematol* 2007;136(1):3–11.
- [72] Martinov MV, Plotnikov AG, Vitvitsky VM, Ataullakhanov FI. Deficiencies of glycolytic enzymes as a possible cause of hemolytic anemia. *Biochim Biophys Acta* 2000;1474(1):75–87.
- [73] Kazemi-Esfarjani P, Skomorowska E, Jensen TD, Haller RG, Vissing J. A non ischemic forearm exercise test for McArdle disease. *Ann Neurol* 2002;52(2):153–9.
- [74] Wanders RJ, Ruiter JP, IJLst L, Waterham HR, Houten SM. The enzymology of mitochondrial fatty acid beta-oxidation and its application to follow-up analysis of positive neonatal screening results. *J Inherit Metab Dis* 2010;33(5):479–94.
- [75] Fernandez-Sola J, Grau JM, Pedro-Botet JC, et al. Non traumatic rhabdomyolysis: a clinical and morphological analysis of 53 cases. *Med Clin (Barc)* 1988;90(5):199–202.
- [76] 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(7):1862–7.
- [77] Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int* 1996;49(2):314–26.
- [78] Sinert R, Kohl L, Rainone T, Scalea T. Exercise-induced rhabdomyolysis. *Ann Emerg Med* 1994;23(6):1301–6.
- [79] 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(6):737–41.
- [80] Better OS, Rubinstein I. Management of shock and acute renal failure in casualties suffering from the crush syndrome. *Ren Fail* 1997;19(5):647–53.
- [81] Antoon JW, Chakraborti C. Corticosteroids in the treatment of alcohol-induced rhabdomyolysis. *Mayo Clin Proc* 2011;86(10):1005–7.
- [82] Hirohama D, Shimizu T, Hashimura K, et al. Reversible respiratory failure due to rhabdomyolysis associated with cytomegalovirus infection. *Intern Med* 2008;47(19):1743–6.
- [83] Yasumoto N, Hara M, Kitamoto Y, Nakayama M, Sato T. Cytomegalovirus infection associated with acute pancreatitis, rhabdomyolysis and renal failure. *Intern Med* 1992;31(3):426–30.
- [84] Heckman MM, Whitesides Jr TE, Grewe SR, Rooks MD. Compartment pressure in association with closed tibial fractures. The relationship between tissue pressure, compartment, and the distance from the site of the fracture. *J Bone Joint Surg Am* 1994 Sep;76(9):1285–92.
- [85] Schaefer J, Jackson S, Dick DJ, Turnbull DM. Trifunctional enzyme deficiency: adult presentation of a usually fatal beta-oxidation defect. *Ann Neurol* 1996;40(4):597–602.
- [86] Bonnefont JP, Demaugre F, Prip-Buus C, et al. Carnitine palmitoyltransferase deficiencies. *Mol Genet Metab* 1999;68(4):424–40.
- [87] Gurnaney H, Brown A, Litman RS. Malignant hyperthermia and muscular dystrophies. *Anesth Analg* 2009;109(4):1043–8.
- [88] Bonnefont JP, Bastin J, Behin A, Djouadi F. Bezafibrate for an inborn mitochondrial beta-oxidation defect. *N Engl J Med* 2009;360(8):838–40.
- [89] Bonnefont JP, Bastin J, Laforet P, et al. Long-term follow-up of bezafibrate treatment in patients with the myopathic form of carnitine palmitoyltransferase 2 deficiency. *Clin Pharmacol Ther* 2010;88(1):101–8.
- [90] Yamaguchi S, Li H, Purevsuren J, et al. Bezafibrate can be a new treatment option for mitochondrial fatty acid oxidation disorders: evaluation by *in vitro* probe acylcarnitine assay. *Mol Genet Metab* 2012;107(1–2):87–91.
- [91] Orngreen M, Madsen K, Preisler N, Andersen G, Vissing J, Laforet P. Bezafibrate does not improve fat oxidation in patients with disorders of fat metabolism; a double blind, randomized clinical trial. *Neuromuscul Disord* 2012;22:852–3.
- [92] Woodrow G, Brownjohn AM, Turney JH. The clinical and biochemical features of acute renal failure due to rhabdomyolysis. *Ren Fail* 1995;17(4):467–74.