A Clinical Approach to Rhabdomyolysis

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Key Points

- Provide a summary on the etiology of exertional rhabdomyolysis
- Provide an overview of the triggers and genetic susceptibilities
- Summarize the (sub) acute management of patients with (exertional) rhabdomyolysis
- Present a diagnostic approach to patients with exertional rhabdomyolysis
- Provide recommendations for daily life and sports to prevent recurrent episodes

Glossary

Creatine kinase (CK) CK is a protein in muscle that is critical for normal energy production, where it catalyzes the reaction between creatine and adenosine triphosphate (ATP) to form phosphocreatine and adenosine diphosphate (ADP). Multiple isoforms of CK are found throughout the body, including skeletal muscle (MM isoform), cardiac muscle (MB isoform), and brain (BB isoform). Some CK leaks from myofibers into the blood under normal physiologic conditions. Normal serum CK level in healthy persons varies and is affected by muscle mass, previous activity level, sex, and ethnicity. CK is higher in men than women and in people of African ancestry compared to those of European or Asian ancestry (Kyriakides et al., 2010). Mean CK values also tend to decrease with age, likely secondary to age-related muscle loss.

HyperCKemia A persistent elevation in serum CK level, at least two standard deviations above the mean expected for a given population on at least two separate occasions. The European Federation of Neurological Sciences (EFNS) defines hyperCKemia as values of more than 1.5 times the upper limit of normal using normative data that factors in sex and ethnicity.

Myoglobinuria Myoglobinuria is the presence of an excess amount of myoglobin in the urine that almost exclusively comes from skeletal muscle breakdown. Myoglobinuria can lead to acute kidney injury. To avoid the high morbidity and mortality associated with this condition, it must be promptly diagnosed and treated.

Rhabdomyolysis Rhabdomyolysis is a complex medical condition involving the rapid breakdown of damaged skeletal muscle. It is clinically characterized by the triad of myalgias, muscle weakness, and red to brown urine due to myoglobinuria. Biochemically, several serum muscle enzymes are elevated, including creatine kinase (CK). The degree of muscle pain and other

symptoms varies widely. It generally results from an interplay between environmental and genetic triggers or acquired susceptibility. One of the most important treatment goals when rhabdomyolysis is suspected is to avoid acute kidney injury.

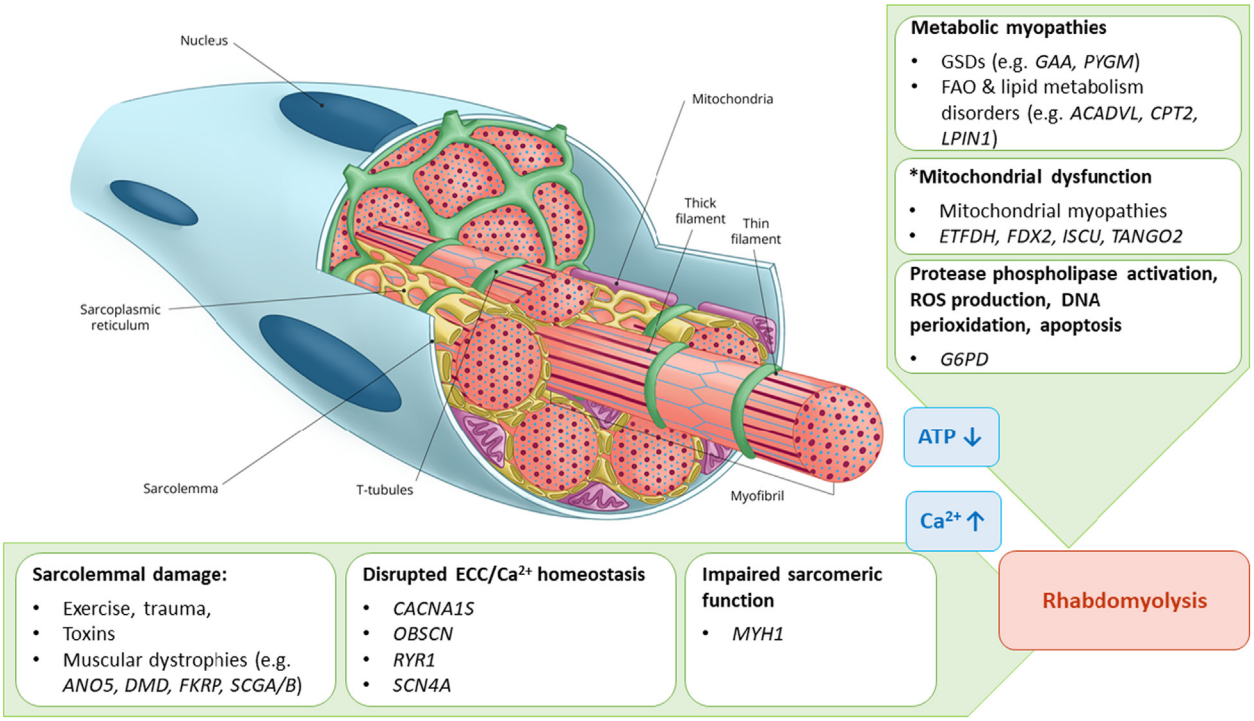
Nomenclature

CK Creatine kinase in U/l

Abstract

Rhabdomyolysis is a medical emergency characterized by acute skeletal muscle breakdown with a sudden strong rise and subsequent fall of serum creatine kinase (CK) levels. Rhabdomyolysis events are provoked by exposure to external triggers, sometimes in combination with an increased genetic susceptibility. In this chapter, we will provide a summary on the etiology of exertional rhabdomyolysis and an overview of the triggers and genetic susceptibilities in adults with rhabdomyolysis, summarize the (sub) acute management of patients with exertional rhabdomyolysis, present a diagnostic approach to patients with exertional rhabdomyolysis, and provide recommendations for daily activities and sports after an episode of rhabdomyolysis to prevent a recurrent episode.

Graphical abstract



Background

This chapter was originally written by a group of experts in preparation for an international workshop to reach consensus on recommendations on optimal diagnostic pathways and management strategies for patients with rhabdomyolysis (ENMC workshop 276, March 15–17, 2024). After the workshop, the content has been streamlined in accordance with decisions reached at this workshop and thus represents the expert opinion of the group of organizers and other participants of the workshop (Tables 1–3).

Table 1 Triggers and genetic susceptibilities contributing to the etiology of rhabdomyolysis (Bosch et al., 2009; Zutt et al., 2014; Nance and Mammen, 2015; Scalco et al., 2016; Cabrera-Serrano and Ravenscroft, 2022; Kruijt et al., 2022). (If the relationship is less clear, the name of the disease is placed between brackets).

	Triggers
Drugs and toxins	Prescribed drugs: Lipid-lowering drugs (fibrates, statins), antidepressants, antihistamines, antipsychotics, anti-retrovirals, colchicine, daptomycin, valproic acid, interferon-alfa, lithium, ofloxacin/levofloxacin
	(Illicit) drugs: Alcohol, heroin, cocaine
Trauma and/or muscle hypoxia	Multiple injury
	Crush injury: Bombings, earthquakes, building collapse, mine accidents, train or motor vehicle accidents
	High-voltage electrical injury
	Extensive third-degree burns
	Vascular/orthopedic 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, immobilization after trauma, anesthesia, coma, drug, or alcohol-induced unconsciousness
Physical exertion	Strenuous exercise
	Seizures
	Cold shivering
	Alcohol withdrawal syndrome (shaking and shivering in delirium tremens)
Infections	Viral: Influenza A and B, coxsackievirus, Epstein—Barr virus, primary human immunodeficiency virus, COVID-19
	Bacterial: legionella species, Streptococcus pyogenes, Staphylococcus aureus (pyomyositis), clostridium
Metabolic changes	Hypokalemia, hyponatremia, hypophosphatemia, hyponatremia, hypocalcemia, nonketotic hyperosmotic conditions, diabetic ketoacidosis
Body-temperature changes	Heat stroke, malignant hyperthermia, malignant neuroleptic syndrome, hypothermia
Genetic susceptibilities	
Disorders of glycolysis or glycogenolysis	Myophosphorylase (glycogenosis type V; McArdle disease)
	Phosphofructokinase (glycogenosis type VII; Tarui's disease)
	Phosphorylase kinase (glycogenosis type VIII) — reclassified as glycogenosis type VI and IXa1
	Phosphoglycerate kinase (glycogenosis type IX)
	Phosphoglycerate mutase (glycogenosis type X)
	Lactate dehydrogenase (glycogenosis type XI)
	Phosphoglucomutase (glycogenosis type XIV)
Disorders of lipid metabolism	Carnitine palmitoyl transferase II
	Long-chain acyl-CoA dehydrogenase [short-chain L-3-hydroxyacyl-CoA dehydrogenase]
	[Medium-chain acyl-CoA dehydrogenase]
	Very-long-chain acyl-CoA dehydrogenase
	Medium-chain 3-ketoacyl-CoA
	Thiolase
	LPIN1 deficiency related disease (LPIN1)
Mitochondrial disorders	Succinate dehydrogenase
	Cytochrome c oxidase
	Coenzyme Q1
	ISCU— and FDX2-related myopathies
	Pentose phosphate pathway: Glucose-6-phosphate dehydrogenase
	Primary mitochondrial myopathies
	Trifunctional protein
Disorders of Ca^{2+} homeostasis	MHS, KDS, other RYR1-related myopathies
	Caveolinopathy (CAV3)
	Obscurin-related rhabdomyolysis (OBSCN) (Cabrera-Serrano et al., 2022; Zemorshidi et. al., 2024)
Other muscle disorders	LGMD's (sarcoglycanopathies, FKRP, DYSF, ANO5, GMPPB)
	Dystrophinopathies (DMD, BMD or carrier state)
	Myosin heavy chain IIX-related rhabdomyolysis (MYH1)
	Muscle lamin A/C interacting protein-related rhabdomyolysis (MLIP)
	ISCU— and FDX2-related myopathies
Other genetic conditions	Sickle cell trait
	Spinocerebellar ataxia type 2 (SCA2)
	DMNT3A-related rhabdomyolysis (Ghaoui et al., 2023)

Table 2 When to refer a patient to the emergency room? This table shows factors that can guide the decision when to refer a patient to the emergency room.

	Outpatient follow-up in case of all features	*Referral to emergency room in 1 or more features*
Clinical features	Only myalgia	Severe myalgia Muscle weakness Muscle swelling Myoglobinuria Reduced consciousness
Vital signs	Normal	Hypotension Tachycardia Body temperature $> 40°$
Known triggers	Yes	No
History		Prior episode(s) of (exertional) rhabdomyolysis Indicators of NMD or sickle cell trait Renal, cardiac comorbidity Illicit drug use
Medication use		Polypharmacy
CK	< 5000 U/l in case of non-exertional rhabdomyolysis $< 10,000$ U/l in case of exertional rhabdomyolysis	$> 10,000$ U/l

Table 3 When to admit a patient to the hospital? This table shows factors that can guide the decision when to admit a patient.

	High-risk factors suggesting inpatient management for rhabdomyolysis is indicated:
Clinical features	Dark urine or confirmed myoglobinuria Potential compartment syndrome
Vital signs	Hypotension Tachycardia Body temperature $> 40°$
History	Sickle cell trait carrier
CK	> 20.000 U/l
Risk of acute kidney injury	McMahon risk score ≥ 5 (McMahon et al., 2013)
Metabolic abnormalities	Hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, acidosis
Other	Limited possibilities for out-patient follow-up

Introduction

Rhabdomyolysis is a complex condition relevant to many medical disciplines, involving the rapid breakdown of damaged skeletal muscle, which can regenerate later. The damaged skeletal muscle membrane leads to the release of intracellular muscle components into the extracellular space, including myoglobin, CK, aldolase, lactate dehydrogenase, electrolytes, and hundreds of other muscle proteins. Clinical manifestations of this muscle damage range from a largely asymptomatic condition with isolated sudden strong rise of serum CK levels, to life-threatening conditions with profound myoglobinuria, potentially leading to acute renal failure, electrolyte abnormalities associated with associated cardiac arrhythmias, and disseminated intravascular coagulation. Definitions vary around the exact CK elevation required to reach the term "rhabdomyolysis". Rhabdomyolysis is commonly and loosely defined as a clinical syndrome of severe myalgias, muscle weakness, and muscle swelling with sudden elevation and subsequent fall of CK levels, with or without the presence of myoglobinuria (**Box 1**) (Bosch et al., 2009; Furman, 2015; Chavez et al., 2016)

Establishing a diagnosis of rhabdomyolysis is based primarily on the combination of these clinical features and the detection of marked elevation of serum CK levels. The appearance of myoglobin in the urine (myoglobinuria) occurs earlier and is not always observed due to the short half-life of myoglobin of 2–3 h (Giannoglou et al., 2007). A recent review summarized the findings on imaging, that can be valuable in evaluating the extent of muscular involvement, MRI shows an increased signal intensity on T2-weighted and STIR sequences and a decreased signal intensity on T1-weighted sequences, reflecting edema (Rixey et al., 2024).

In a case series of 37 pediatric patients with a mildly elevated CK (>1000 U/L), the most common presenting symptoms were myalgia (84%), muscle weakness (73%), and muscle swelling (8.1%) (Chen et al., 2013). In our retrospective study of 1302

Box 1 The key features of rhabdomyolysis

1. A CK elevation **12–36 h after the trigger**, with a maximum at 1–4 days post-exercise or other trigger, followed by normalization within several weeks of rest.
2. The elevation of CK to meet the definition of rhabdomyolysis is not universally agreed upon, but should as a minimum be
   - **> 25 times the upper limit of normal (>5000 U/l)** in case of non-exertional rhabdomyolysis
   - **> 50 times the upper limit of normal (>10,000 U/l)** in case of exertional rhabdomyolysis (Kenney et al., 2012; Stahl et al., 2020).
3. The CK increase is preceded by exercise (usually beyond the limits of fatigue, also referred to as "unaccustomed physical exertion" or "involuntary exertion") and/or one or more other trigger(s) (long lay, alcohol consumption (illicit) drug abuse)
4. The CK increase is **symptomatic** with any of the following features: severe myalgia (severe muscle soreness or tenderness), swelling, and/or weakness
5. The presence of **myoglobinaemia and/or myoglobinuria**: either by inspection (pigmenturia) or by laboratory testing. Since myoglobin testing in blood or urine is not widely available, many experts consider the combination of the other features diagnostic for rhabdomyolysis (CK increase, severe myalgia, muscle swelling, and/or weakness)

patients with a CK > 2000 U/l, 193 patients were identified with an increased likelihood of having a genetic susceptibility based on presence of one or more RHABDO features (see **Box 2**) (age range 0–94; median age 31 years). Prevalence of symptoms in this group was: myalgia and/or muscle cramps (85%); muscle stiffness (39%); muscle weakness (67%), muscle swelling (54%), and reported myoglobinuria (45%) (Kruijt et al., 2022).

After acute muscle injury, myoglobin is the first protein that increases, likely since myoglobin is about a fourth the size of CK. It is cleared quickly through renal excretion and generally returns to normal levels within the first 24h. In contrast, serum CK levels rise 2–12 h after onset of muscle injury, and peak at 1–5 days after the injury, and decline over the subsequent days (**Fig. 1**) (Giannoglou et al., 2007). The peak time is dependent on the muscle insult, for instance, eccentric strength training vs. aerobic challenge. Furthermore, in inherited myopathies with a high susceptibility of developing rhabdomyolysis, CK peaks earlier than in healthy individuals. In a recent study on the biomarker response to injury, peak levels of CK in persons with Becker muscular dystrophy (BMD), Limb girdle muscular dystrophy R9 (formerly LGMD2I) FKRP-related), and McArdle disease were observed after 4 h. In healthy individuals, the CK peak was generally observed 3 to 5 days after heavy exercise as stated (Stemmerik, personal communication). Hence, even though the presence of myoglobin in serum is the key feature of rhabdomyolysis, CK is a more useful marker for the diagnosis and assessment of the severity of muscular injury due to its delayed clearance from the plasma and the wide availability for diagnostic testing.

Rhabdomyolysis is not a monogenetic condition but an event resulting from the combination of exposure to trigger(s) and sometimes one or more genetic susceptibilities. It can involve multiple organ systems including renal, cardiac, pulmonary, and neurologic requiring multidisciplinary medical and potentially, surgical care. Consequently, expertise on the optimal diagnostic pathway and management strategy is not centered within one medical specialty, but rather scattered across several disciplines.

A study on the CK levels in military service shed light on the "**physiological response" of healthy muscle to unaccustomed physical exercise.** The spectrum of CK responses in military recruits (n = 449) undergoing basic military training was assessed at days 0, 3, 7, and 14 of training. None of the persons developed clinical signs of exertional rhabdomyolysis. The mean/median serum CK values were 223/157, 734/478, 1226/567, and 667/486 IU/L at days 0, 3, 7, and 14, respectively, with a wide overall range (34–35,056 IU/L). African-American subjects had higher mean CK levels. The authors concluded that CK elevations and muscle pain are common during basic training. Widely accepted laboratory diagnostic values for exertional rhabdomyolysis are routinely exceeded in these military recruits, suggesting that CK levels >50 times the upper limit of normal are more specific (Kenney et al., 2012). Even higher levels of CK (up to 200,000 U/l) have been reported in healthy individuals following unaccustomed, eccentric training (Chen et al., 2020). These results of this study by Chen et al. suggest that plasma troponin I (TnI) concentrations are more specific biomarkers of muscle damage than serum CK activity and myoglobin concentration. It seems that the whole-body eccentric

Box 2 Consider a genetic cause of the exertional rhabdomyolysis in case of any of the "RHABDO" features

R: Recurrent episodes of exertional rhabdomyolysis.
H: HyperCKemia persists 8 weeks after the event.
A: Accustomed physical exercise: the intensity of the exercise cannot explain the rhabdomyolysis event.
B: Blood CK > 50×ULN (>10,000 ULN).
Drugs/medication/supplements and other exogenous and endogenous triggers cannot sufficiently explain the rhabdomyolysis severity.
O: Other family members affected/Other exertional symptoms (cramps, myalgia).
ULN: upper limit of normal.

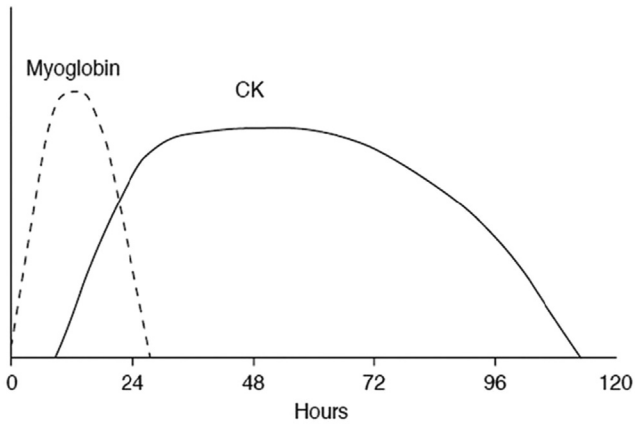


Fig. 1 Rise and fall of myoglobin and creatine kinase (CK) during an episode of rhabdomyolysis. Reprinted from Giannoglou et al. (2007) Copyright 2007, with permission from Elsevier.

exercises induced damage preferentially to fast-twitch muscle fibers and increases in serum CK activity and myoglobin concentration after eccentric exercise may reflect fast-twitch muscle fiber damage.

Considering the increasing incidence of exertional rhabdomyolysis (Liu et al., 2020; Boden et al., 2022), a consensus on the optimal diagnostic pathway and management strategy for patients with exertional rhabdomyolysis worldwide is highly needed.

The Pathophysiology of Exertional Rhabdomyolysis

Exertional rhabdomyolysis is increasingly recognized as the result of the combination of a genetic susceptibility and exposure to triggers (Fig. 2). In patients with a genetic susceptibility, the trigger might be very mild and remain unnoticed (Cabrera-Serrano et al., 2022). At the same time, individuals without a genetic susceptibility may develop rhabdomyolysis when exposed to extreme triggers. The simultaneous occurrence of rhabdomyolysis of players of various sports teams illustrates the role of physical exertion as trigger. These team members do not share a common genetic background but were exposed to the same overexertion (Eichner, 2018).

Irrespective of its cause(s), the pathophysiological events in rhabdomyolysis follow a common pathway (Fig. 3). Normally, ion pumps and channels in the sarcolemma maintain a low intracellular Na^+ and Ca^{2+} and a high intracellular K^+ concentration. Unaccustomed exercise may cause direct injury to the sarcolemma and/or lead to failure of energy production with subsequent pump dysfunction of Na^+/K^+ ATPase and Ca^{2+}ATPase (e.g., in eccentric exercise or prolonged training beyond the limit of fatigue). These

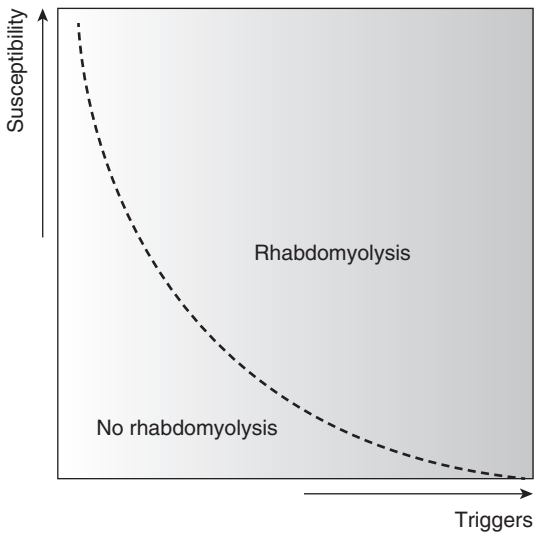


Fig. 2 Graph showing that rhabdomyolysis events can be attributed to a combination of environmental factors (e.g., strenuous exercise and/or febrile infection) and a predisposing genotype. A combination of external triggers and genetic predisposition may thus be required for an individual to exceed the threshold for developing rhabdomyolysis. Modified from Kruijt et al. (2021).

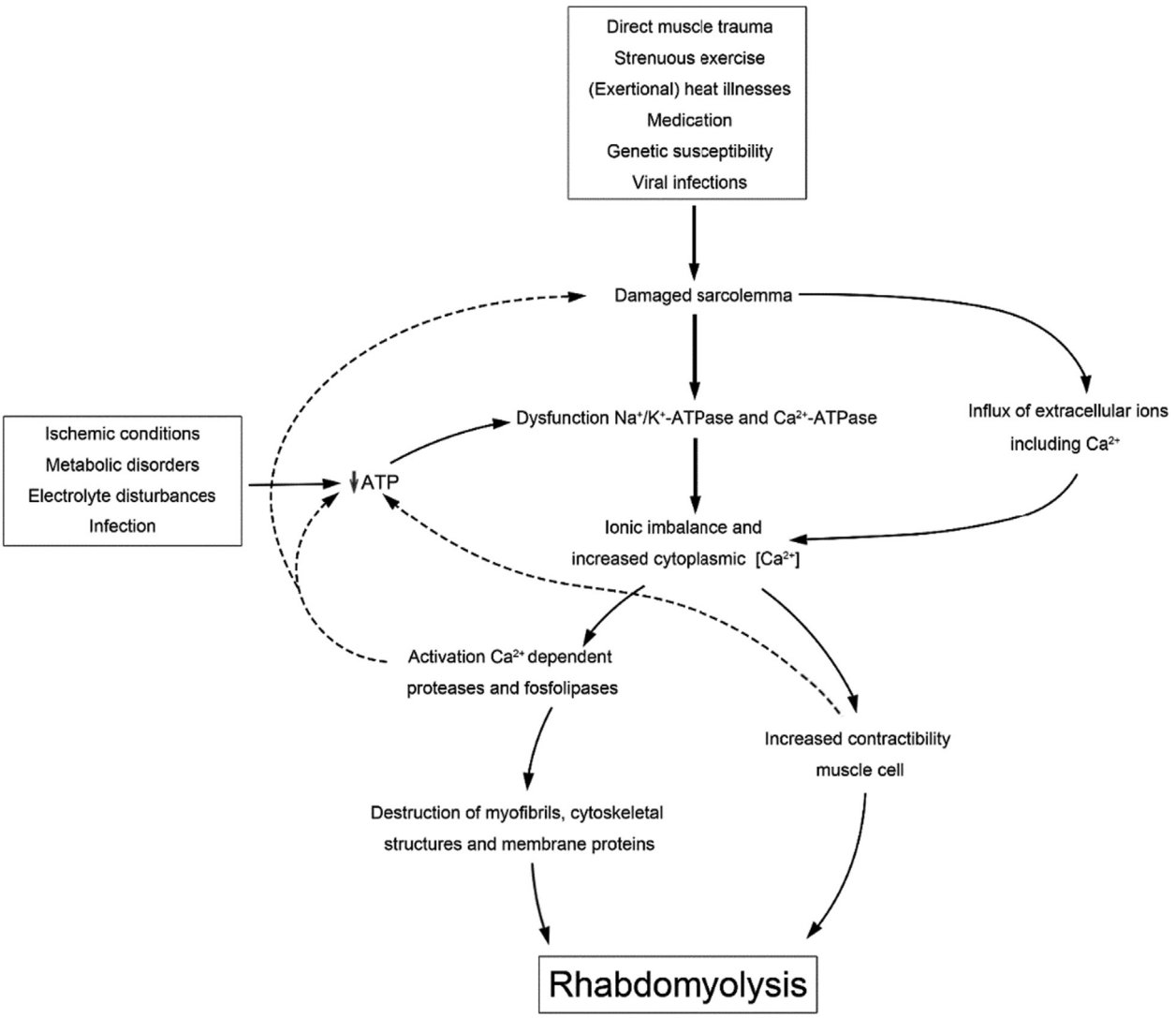


Fig. 3 Pathophysiology of rhabdomyolysis. The pathophysiological events in rhabdomyolysis follow a common pathway, irrespective of its cause. CK, creatine kinase; SR, sarcoplasmic reticulum. Adapted from Kruijt et al. (2022).

processes lead to increased cellular permeability to sodium ions and, consequently, increased intracellular Ca^{2+} concentrations, with concordant muscle contraction increasing the energy deficit. This increased intracellular Ca^{2+} concentration enhances the activation of Ca^{2+}-dependent proteases and phospholipases, which lead to destruction of myofibrillar, cytoskeletal, and membrane proteins. Subsequently, large quantities of intracellular electrolytes, metabolites as well as intracellular proteins (aldolase, myoglobin, CK, lactate dehydrogenase, aspartate transaminase) leak into the circulation. The resulting free Ca^{2+} will add to the contraction of the already overactivated surrounding myofibers, resulting in a vicious circle of contraction and myofiber breakdown.

Fluid sequestration by damaged muscle leads to profound intravascular volume depletion. This shift may, over the course of the illness, exceed 15L and exacerbate the potential for acute renal failure. Potassium release from muscle cells during exercise normally mediates vasodilation and an appropriately increased blood flow to muscles. Decreased potassium release due to profound hypokalemia (serum potassium <2.5 mEq/L) worsens rhabdomyolysis by decreasing blood flow to muscles in response to exertion, thus limiting availability of energy sources.

As rhabdomyolysis progresses, hyperkaliemia develops, which can result in fatal cardiac arrhythmias. Hyponatremia contributes to Na^{+}/Ca^{2+}-ATPase dysfunction, which leads to the activation of proteases and lipases that are responsible for further cell lysis. Furthermore, hyponatremia causes failure of cell volume regulation, leading to exertional cell lysis that may stimulate vasopressin secretion. Thus, rhabdomyolysis may occur during the development of hyponatremia, or during its correction. Combined with other cellular responses to exercise such as increased oxidative stress and release of proinflammatory cytokines, this will ultimately result in cell death and intracellular components spilling into the surrounding tissue.

Myoglobin, the hemoprotein that functions as an oxygen carrier in striated and cardiac muscle, is normally bound to plasma globulins. In the case of rhabdomyolysis, myoglobin leaks from the myofiber and immediately peaks to levels that exceed the plasma protein-binding capacity. Myoglobin then precipitates in the glomerular filtrate and obstructs renal tubules, an important factor in the pathogenesis of acute renal failure. Other factors contributing to acute renal failure include vasoconstriction, hypovolemia and a direct renal toxic effect of myoglobin.

Triggers and Genetic Susceptibility

Retrospective cohort studies on rhabdomyolysis in hospitalized patients, before next generation sequencing was available, focused mainly on external triggers as the major cause for the rhabdomyolysis event (Melli et al., 2005; Linares et al., 2009; Herraez Garcia et al., 2012). In 2005, Melli et al. described the features of 475 patients with rhabdomyolysis in the USA (CK > 1000 U/l), reporting exogenous toxins (illicit drugs, alcohol and medicinal drugs) as the most common trigger, followed by traumatic muscle injury (Melli et al., 2005). Linares et al. described a series of 106 hospitalized patients in USA with rhabdomyolysis (CK > 5000 U/l), reporting recreational drug and/or alcohol use (28%), trauma (23%), compression (19%), shock (17%), statin-use (13%), seizure (8%), and quetiapine-use (8%) as the most common triggers. In 37% of the patients, multiple triggers were reported (Linares et al., 2009). In a Spanish series of 449 patients, most frequent etiologies were trauma, sepsis, and immobility/crushing (24, 19 and 17% respectively) (Linares et al., 2009). In addition, a wide range of sports activities have been associated with exertional rhabdomyolysis, both in recreational and professional athletes, military personnel, policemen, and firemen. Exertional rhabdomyolysis has been reported in various members of a sports team simultaneously. Recently the features of 17 episodes of team exertional rhabdomyolysis in sports were summarized: seven in football, two in swimming, two in lacrosse, and one each in soccer, track, basketball, softball, volleyball, and even golf. In each case, the cause was overexertion after abstaining from exercise for a long time: too much, too soon, too fast. In all cases, to a greater or lesser degree, the culprits were the coaches (Eichner, 2018).

Regarding the presence of a genetic susceptibility, most of these studies are biased by recruiting patients from emergency rooms and intensive care units, likely underrecognizing genetic causes, which were more difficult to diagnose as the diagnostic tools to detect a genetic contribution were at that time not widely available. In general, when the external triggers are obvious, such as identified in the study of Melli, patients are less frequently referred to a geneticist or neurologist for ancillary investigations.

We have recently performed a retrospective hospital-based single-center study, including a total of 1302 patients with an acute CK level exceeding 2000 IU/l, assessing both reported triggers and results on ancillary testing (Kruijt et al., 2021). Ischemia/anoxia (including vascular occlusion, thrombo-embolism, shock, aortic dissections, or asphyxia) was the most frequently reported trigger (40%). A subset of 193 patients were clinically suspected of having an underlying genetic disorder (based on the RHABDO features) (Scalco et al., 2016). In 72 of them, an underlying genetic susceptibility was identified (52 different variants in 22 genes). Eleven genes had previously been associated with rhabdomyolysis (*genes associated with metabolic or mitochondrial myopathies*: *ACADVL, CPT2, PGM1, LPIN1, PYGM; genes associated with muscular dystrophies: ANO5, DMD, DYSF, FKRP; and genes associated with abnormal* Ca^{2+} *homeostasis RYR1*). Eleven genes were considered likely to be implicated in increased susceptibility (*genes associated with metabolic or mitochondrial myopathies*: including *AGL, ACADM, TANGO2; genes associated with muscular dystrophies: CAPN3, CNBP, DMPK, SCN4A, SGCA, SGCG; and others MAGT1, SMPD1*). These findings suggested that the spectrum of genetic susceptibility for rhabdomyolysis has not yet been completely clarified.

This study also illustrates that the availability of diagnostic next generation sequencing has led to the identification of novel underlying genetic disorders and has increased the awareness that rhabdomyolysis may be attributed to a combination of environmental factors and a predisposing genotype. The main categories of triggers and genetic susceptibilities are listed below. We refer to recent reviews for a description of the clinical features and results of ancillary investigations of these genetic conditions (Landau et al., 2012; Scalco et al., 2016; Cabrera-Serrano and Ravenscroft, 2022).

(Sub)acute Management of Adult Patients With Exertional Rhabdomyolysis

When to Refer a Patient to the Emergency Room?

The first step when encountering a patient with symptoms and signs suggestive of rhabdomyolysis is to determine whether the rhabdomyolysis requires referral to an emergency room and intravenous fluid administration. There are no convincing trials providing concrete management guidelines for this question or other aspects of rhabdomyolysis treatment.

In 2020, a multidisciplinary team of the U.S. Department of Defense revised and updated a clinical practice guideline to assist providers in evaluating and managing military personnel (https://www.hprc-online.org/resources-partners/whec/clinical-care/clinicalpractice) (Nye et al., 2021). This guideline is based on published evidence and expert consensus opinion. Nye et al. subsequently published a summary of this guideline in *Current Sports Medicine Reports* to introduce it to the greater military and sports medicine communities to highlight the military's approach to challenging clinical questions and particular areas of clinical controversy (Nye et al., 2021). This is in line with our previous recommendations (Scalco et al., 2016) and the consensus reached during the workshop.

Recommendations for outpatient follow-up of patients with (EXERTIONAL) RHABDOMOYLYSIS by the neurologist or ER specialist

- Rest for 72 h and encourage oral hydration (without caffeine)
- Sleep 8 h consecutively, nightly
- Remain in thermically controlled environment if rhabdomyolysis occurred in association with heat injury
- Refer to emergency room in case body temperature exceeds 40 °C
- Follow-up in 72 h for repeat creatine kinase (CK) and blood urea (this could be assessed remotely):
  - CK $<$ 5 $\times$ upper limit of normal (ULN) and normal blood urea: no further studies
  - Return every 72 h and repeat until CK $<$ 5$\times$ULN and normal blood urea
  - CK $\geq$ 5$\times$ ULN or abnormal blood urea for $>$ 2 weeks: refer for expert consultation
  - CK $\geq$ 50 $\times$ ULN (10,00U/L): refer to emergency room again
- Refrain from sports
- Elimination of medications, drugs and toxins that are considered to cause rhabdomyolysis

When to Admit a Patient to the Hospital?

The second step takes place during evaluation in the emergency room: does the patient require further inpatient management? The clinical practice guideline from the Department of Defense presents a number of risk factors for which inpatient management is required.

Recommendations for inpatient follow-up of patients with rhabdomyolysis (Sawhney et al., 2022)

- Hyperhydration: Intravenous fluids should be initiated as soon as possible, preferably within the first 6 h after muscle injury, at a rate that maintains a urine output in adults of $\geq$300 mL/hours for at least the first 24 h
- Admit at an ICU and consider peritoneal dialysis or hemodialysis in patients with little or no urine output despite hyperhydration, profound acidosis or severe hyperkaliemia
- Sodium bicarbonate should be administered only if necessary to correct systemic acidosis
- Elimination of medications, drugs and toxins that are considered to cause rhabdomyolysis
- Mannitol should not be administered (Sawhney et al., 2022)

What is the Risk of Developing Acute Renal Failure?

The third step concerns the assessment of the risk of acute renal failure and mortality, according to the McMahon algorithm (McMahon et al., 2013). It has been developed from a retrospective analysis, and subsequently been validated in a prospective cohort (Simpson et al., 2016). This algorithm shows that the risk of acute renal failure increases with a CK $>$ 40,000 IU/L (McMahon et al., 2013). Other risk factors are age $>$50 years, female sex, initial creatinine $>$1.4 mg/dL, and additional metabolic changes (hypocalcemia, hyperphosphatemia, decreased bicarbonate) (**Fig. 4**). Creatine kinase is not a specific or early predictor of acute renal failure in patients with rhabdomyolysis. Hence, although a peak creatine kinase of at least 5000 U/l has sensitivity acceptable for screening purposes, this is often a delayed finding. Instead, a McMahon risk score, calculated on admission, of 6 or greater is predictive of AKI requiring renal replacement therapy. Treatment of the underlying cause of the muscle insult is the first component of rhabdomyolysis management.

The ability to identify these patients early during a rhabdomyolysis episode is useful for the decision on ICU admission, early start of aggressive prophylactic measures, admission to the ward or intensive care unit, and communication with patients and families about prognosis. The clinical practice guideline also presents guidelines for inpatient management of acute rhabdomyolysis, a topic beyond the scope of this review (Nye et al., 2021).

Diagnostic Approach to Adult Patients With Exertional Rhabdomyolysis

So far, several Mendelian genetic defects have been identified to increase rhabdomyolysis susceptibility, including several genes implicated in muscle metabolism and mitochondrial function (e.g., *ACADVL*, *CPT2*, *PYGM* or *LPIN1*), genes associated with muscular dystrophies (e.g., Becker muscular dystrophy and limb girdle muscle dystrophy R9 (formerly LGMD2I), or genes associated with congenital myopathies due to defects in Ca^{2+} homeostasis and excitation-contraction coupling (e.g., *RYR1*). Such marked genetic heterogeneity poses a considerable diagnostic challenge for clinicians. The awareness of specific genotype−phenotype correlations is of great importance, not only for establishing the correct genetic diagnosis, but also for effective personalized counseling. The means to detect a genetic contribution have increased markedly since the introduction of next-generation sequencing.

To identify episodes of rhabdomyolysis suggestive of an underlying genetic susceptibility, we have introduced the acronym RHABDO (BOX X) (Scalco et al., 2016). It aims to distinguish the patients in whom the external triggers are (largely) sufficient to explain the episode of rhabdomyolysis from those in whom the external triggers insufficiently explain the (severity of the) rhabdomyolysis event, increasing the likelihood of an underlying genetic susceptibility. It was composed based on an extensive review of the literature and expert opinion and has been adopted by others (Fernandes and Davenport, 2019; Gupta et al., 2021; Cabrera-

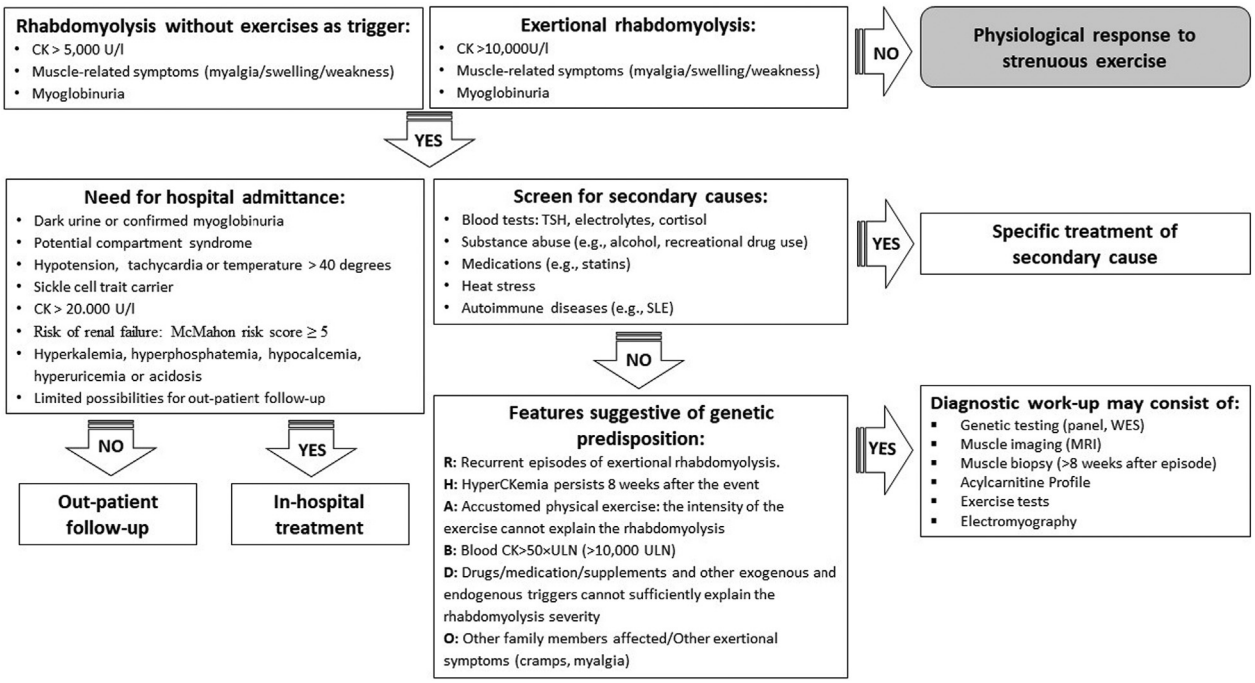


Fig. 4 Flowchart for treatment and screening of patients with rhabdomyolysis.

Serrano and Ravenscroft, 2022). It has not been tested prospectively, but we have used it in our retrospective case series (Kruijt et al., 2022).

In case of one of these features, we recommend genetic testing covering neuromuscular and metabolic diseases. In case this is negative or equivocal, additional ancillary investigations (further genetic testing, muscle MRI, muscle biopsy (>8 weeks after episode), acylcarnitine profile, exercise tests) should be considered. This approach is summarized in the flowchart in **Fig. 4** (McMahon et al., 2013; Fernandes and Davenport, 2019).

Recommendations for Restarting Physical Activity to Prevent Recurrent Episodes

No evidence-based guidelines concerning return to physical activity after (exertional) rhabdomyolysis are currently available. The natural course of (exertional) rhabdomyolysis in cases without suspicion of a genetic disorder suggests that return to sports is safe. During follow-up (ranging from 20 to 60 months, mean of 31.2 months), there was only one recurrence of rhabdomyolysis (at 1 month following exertion) in this cohort, yielding a recurrence risk of 0.08% per person per year.

Several expert opinion guidelines advise refraining from sports for at least 4 weeks, until the CK has normalized, and then resuming light activities. In military and sports medicine, four phases of return to physical exercise for soldiers or athletes who are not at risk can be distinguished (O'Connor et al., 2008; Nye et al., 2021): Phase 1: do not restart activities until normalization of CK to <5 times the ULN; Phase 2: Start light activities; Phase 3: Gradually return to regular sporting activities and physical training; and Phase 4: Return to full participation (Nye et al., 2021). The recommendations below are based on these guidelines.

Patients without suspicion of a genetic disorder:

- Advice to restart sport >4 weeks of the event and patient is asymptomatic.
- Start light but no strenuous physical activities
- Follow-up with physician in 1 week
- In case of clinical symptoms (muscle weakness, swelling or myalgia) remain in start schedule and return at 1-week intervals
- Only if no clinical symptoms (muscle weakness, swelling or myalgia) return, gradually increase the intensity and duration
- Avoid unaccustomed exercise, especially eccentric training
- Follow-up with care provider as needed

Additional recommendations for patients with (suspicion of) a genetic disorder in general:

- Search help of a physical therapist/sports medicine specialist/rehabilitation specialist with expertise of training in inherited myopathies
- Wear an SOS necklace
- Very gradual return to a less-intense training schedule

- Strictly avoid the combination of strenuous exercise with other risk factors for rhabdomyolysis (drugs, medication, supplements, viral infection)
- Strictly avoid unaccustomed exercise, especially eccentric training
- Prevent dehydration during exercise
- Limit training intensity in hot and humid environment
- Report to physician in case of exertional myalgia and perform creatine kinase check-up

Additional recommendations for patients (with suspicion) of metabolic myopathies:

- Prevent fasting (especially in fatty acid disorders of lipid metabolism)
- Avoid sugar intake just before exercising (Tarui's disease)
- Consider sugar intake just before exercising (in case of McArdle disease or PGM1 deficiency)
- Wait until "second wind" before increasing exercise intensity (McArdle disease)
- Avoid exercising if catabolic stress, e.g. infection (fatty acid oxidation disorders)

Additional recommendations for patients (with suspicion) of type 1 ryanodine receptor (RYR1)-related exertional rhabdomyolysis (expert opinion):

- Prevent the combination of extreme heat exposure and strenuous exercise
- Do not use caffeine or other supplements
- Limit alcohol consumption, especially in periods of intense sport activities

Additional recommendations for patients (with suspicion) of sickle cell trait:

- Patient should be asymptomatic
- Prevent dehydration before, during and after exercise
- Do not use caffeine, other supplements, or drugs prior to exercise without medical advice
- Avoid exercising in the presence of other triggers for sickle cell trait-related rhabdomyolysis (hot and humid weather, high altitude, concomitant infection, etc.)
- Assess previous history of exercise collapse associated with sickle cell trait for further advice

Conclusion

We have here presented an overview of clinical and diagnostic aspects of exertional rhabdomyolysis, in a stepwise approach. At each step, it is important to distinguish the role of triggers and a possible genetic susceptibility. It is essential for physicians working at the "physiological" end (sports medicine/military medicine) and those working at the clinical end of the medical spectrum (emergency medicine, internal medicine, neurology) to consider that exertional rhabdomyolysis can happen to anyone who is exposed to unaccustomed exercise and/or other triggers. The threshold, however, is much lower in patients with an underlying genetic disorder (Scalco et al., 2016). The acute management of patient with rhabdomyolysis includes a stepwise approach: (1) When to refer a patient to the emergency room?; (2) When to admit a patient to the hospital?; (3) What is the risk of developing acute renal failure? In the subacute phase, the RHABDO acronym can be of help to select patients for ancillary investigations. Finally, patients should be supported in restarting their activities.

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USA Warrior Heat- and Exertion-Related Events Collaborative. The Warrior Heat- and Exertion-Related Events Collaborative is a multidisciplinary advisory group focused on developing and implementing procedures to help providers, Service Members, and civilians prevent and treat heat-related illnesses and injuries. WHEC works in collaboration with the Army Heat Center at Fort Moore, GA, and USU's Multidisciplinary Case Review Committee (MDCRC). https://www.hprc-online.org/resources-partners/whec. (This website contains the link to the Inpatient Management of Exertional Rhabdomyolysis Practice Recommendation).

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