

## Treatment of exertional rhabdomyolysis among athletes: a systematic review protocol

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### Review question/objective

The objective of this review is to identify effective treatment methods associated with exertional rhabdomyolysis in athletes.

The review questions are:

- Among athletes, is fluid resuscitation/replacement or nutritional intervention more effective in treating exertional rhabdomyolysis?
- Does one specific method of fluid resuscitation/replacement lead to decreased time to return to physical activity when compared to another?
- Does length of hospital stay influence time to return to activity?

### Background

Exertional rhabdomyolysis (ER) is a breakdown of skeletal muscle tissue induced by exercise. It is defined as “a clinical and biochemical syndrome, resulting from skeletal muscle injury that alters the integrity of the muscle cell membrane sufficiently to allow the release of muscle cell contents into the plasma”.<sup>1</sup> The release of muscle proteins into circulation, particularly creatine kinase (CK) and myoglobin may result in acute renal failure and possibly death.<sup>2</sup> The incidence of rhabdomyolysis has been reported to be approximately 26,000 cases per year in the United States; though the exact number of those classified specifically as exertional in nature is unknown.<sup>3</sup> While ER is typically caused by a crush injury or drug toxicity, these mechanisms for the development of the condition are not frequently

seen in the athletic population. Reports of ER in the military are numerous; however the incidence in trained and untrained adults and older teens is increasing.<sup>2</sup> In the athletic population, this condition is of great concern given the high incidence of death if not treated quickly and effectively. Furthermore, athletes carrying the sickle cell trait are at increased risk for the development of this condition, particularly during the first few days of intense exercise.<sup>4</sup>

There does not seem to be a conclusive set of criteria for the diagnosis of ER. Several features should be considered in each suspected case: an event of muscle destruction, an increase in serum levels of skeletal muscle enzymes, an increase in serum myoglobin levels and the presence of myoglobin in the urine, or myoglobinuria, which presents as a reddish brown urine.<sup>5</sup> Non-specific complaints include muscle pain (myalgia) and weakness, muscle stiffness, and swelling.<sup>5</sup>

In order to establish the presence of ER, it is helpful to determine the timeframe of symptom onset and identify other signs such as the aforementioned severity of muscle soreness and changes in urine color.<sup>6</sup> It is common in group-based exercise, such as athletics, for energy exertion to persist beyond the point of fatigue, which may contribute to the development of ER.<sup>7</sup> These vigorous bouts of exercise may coincide with factors that cause renal dehydration, heat-related illness, and sickle cell trait. Individuals carrying the sickle cell trait may have a decreased ability to conserve water during strenuous activity, particularly in a high heat environment, nor can they properly concentrate urine, thus leading to limited renal blood flow.<sup>4,8</sup>

Typically, a history of strenuous exercise can be identified by the presence of factors that contribute to muscle breakdown, such as eccentric (lengthening) muscle contractions or repetitive, strenuous exercise.<sup>9,10</sup> Significant muscle soreness that cannot be attributed to general soreness from a workout, occurs 24-48 hours post-exercise, and is typically identified as Delayed Onset Muscle Soreness (DOMS), is also an indication of ER.<sup>10</sup>

When diagnosing ER, blood tests often demonstrate elevated muscle enzymes, specifically creatine kinase (CK). There are three types of CK isoenzymes in human tissue, each located within a specific type of tissue, either the brain, lungs, heart or skeletal muscle.<sup>1</sup> The muscle enzyme CK-BB (or CPK-1) is predominantly found in brain and lung tissue, CK-MB (or CPK-2) is primarily found in cardiac tissue but also exists in skeletal muscle, while CK-MM (CPK-3) is located within skeletal muscle tissue.<sup>1</sup> A CK level of 20,000 U/L or greater has been shown as the threshold value to begin treatment. If CK-MB exceeds 5% of the total CK activity, there could potentially be involvement of the myocardium thus warranting additional cardiac diagnostic tests.<sup>1,7</sup> Although myocardial involvement is not a typical sequelae of ER, progression to include this condition could impact morbidity. Other literature suggests that a CK level greater than 10-times the upper limit of the normal range should be used to determine the necessity of hospitalization.<sup>10</sup> Baseline serum CK levels can vary depending on race, gender, and physical activity levels.<sup>7</sup> Unlike cardiovascular conditions, CK levels are not typically evaluated during the pre-participation examination; therefore, it is difficult to use this value as an absolute indicator of ER. Instead, it is used to assist in differentially diagnosing the condition from sickle cell crisis, DOMS, and muscle strains.<sup>11</sup>

An additional diagnostic indicator of ER is evident when a patient presents with myoglobinuria. This condition occurs when myoglobin is released into the bloodstream following muscle damage, enters the urine and reaches a plasma concentration exceeding 15 mg/l. It has been found that myoglobin has a nephrotoxic effect and may cause renal constriction and ischemia, myoglobin cast formation, and has a

direct cytotoxic action on epithelial cells of the proximal convoluted tubules.<sup>5</sup> These complications, along with increased CK levels and dehydration, may lead to acute renal failure.<sup>10</sup>

While ER may present with myoglobinuria, this sign may not exist in all cases. Furthermore, it should be noted that myoglobinuria does not exist without rhabdomyolysis and is therefore an important factor in the diagnosis of this condition. Increased serum myoglobin levels will often precede increased serum CK levels, but myoglobin levels can return to normal within 1 to 6 hours after termination of the activity that led to muscle injury. Myoglobin serum and urine levels have been used as early diagnostic factors, and thus the absence of these elevated levels has been shown to be effective in excluding a diagnosis of ER.<sup>1</sup>

Early recognition of the signs and symptoms of ER should occur to best initiate appropriate fluid replacement, ensuring permanent damage to the vital organs is minimized and to secure the best possibility of a prompt return to regular activity. In the athletic population, particular attention should be paid to recognizing ER signs and symptoms in persons known to be carrying the sickle cell trait and participating in strenuous exercise in heated environments,<sup>12,13</sup> as they are at an increased risk of developing ER.

There are several factors that are uncertain in the recognition and treatment of ER. Baseline CK levels are of concern during the process of differential diagnosis however, they are not currently measured in athletes prior to participation in exhaustive exercise. This lack of baseline measure therefore makes it difficult to establish when a 5% increase in these values has occurred. Additionally, CK levels cannot be measured on the field; they must be determined in a hospital setting and thus, a delay in diagnosis and treatment may occur.

Following diagnosis of ER, fluid replacement/resuscitation is typically achieved through introduction of intravenous (IV) fluids. The primary goal of early fluid replacement is to preserve renal function and this is typically accomplished through the administration of normal saline (NS) given at a rate of 1.5 mL/hr.<sup>14,15</sup> While the administration of saline is accepted for treatment of ER, the literature is inconsistent in determining if isolated saline administration is best practice, or if combined saline and other pharmacological and/or nutritional interventions improve patient recovery and return to physical activity.

Several options have been identified in the literature as factors to consider during the treatment of ER. For example, it has been suggested that when CK levels have decreased to a level at or below 1,000 units per liter, 1-2 ampules of Sodium Bicarbonate may be added to the saline.<sup>15</sup> The addition of the Sodium Bicarbonate is used for alkalization of the urine which has been shown to decrease the toxicity of the myoglobin to the tubules.<sup>14-16</sup> Alternately, the use of Mannitol to increase renal flow has been discussed by several authors, but overall results are inconclusive.<sup>14-16</sup> It is believed that urinary output should be maintained between 200-300 mL/hr until myoglobinuria has ceased; though at this time it is unclear how this output is influenced by the practice of combining fluid replacement methods.<sup>14,15</sup>

Once treatment is initiated, it is not known what volumes of fluid replacement and nutritional interventions are best practice, in order to ensure return to normal CK and myoglobin levels within the body, as current literature has yet to demonstrate a conclusive algorithm for the treatment of rhabdomyolysis or the more specific form, ER.<sup>10</sup> As a result, the average time to return to normal body function, and ultimately return to regular physical activity, is also yet to be determined. It is important to

identify which method is best in minimizing organ damage, length of time a patient is hospitalized, and also in maximizing the opportunity for return to play. No randomized controlled trials have been conducted comparing fluid replacement/resuscitation methods in patients experiencing ER, and triangulation of literature to this point has not consistently demonstrated that one method is superior to others.

The purpose of this review is to evaluate the treatment of ER among athletes. Specifically, the effectiveness of fluid resuscitation/replacement versus nutritional interventions will be examined as well as the potential influence of treatment on time to return to activity. An initial review of the Cochrane Library, JBI Database of Systematic Reviews and Implementation Reports, CINAHL and other relevant databases did not reveal any current or planned reviews on this topic.

## **Keywords**

athlete; creatine kinase; exertional rhabdomyolysis; fluid resuscitation; myoglobin

## **Inclusion criteria**

### ***Types of participants***

The quantitative review will consider studies that include adolescent and adult patients (15 years and older), specifically athletes, diagnosed with exertional rhabdomyolysis. The minimum age of 15 has been selected due to the high number of adolescents participating in athletics.

### ***Types of interventions***

The review will examine studies or case reports that include fluid resuscitation/replacement or other treatment methods of exertional rhabdomyolysis. Specifically, studies that utilized saline intravenous resuscitation will be sought. Intravenous solutions combining saline with other pharmacological agents, such as sodium bicarbonate, will be included. Any additional treatment methods found in the literature, such as nutritional interventions, will be evaluated as well.

### ***Types of Outcomes***

Studies will be considered if they include one of the following outcome measures: amount/type of fluid resuscitation/replacement, length of hospital stay, and length of time from diagnosis to return to pre-morbid levels of physical activity.

### ***Types of studies***

Due to the absence of RCTs, the quantitative component of the review will consider descriptive studies, case series and individual case reports for inclusion. Identified studies will be evaluated for current best practice evidence regarding the treatment of ER.

## **Search strategy**

To obtain the necessary literature for this review, a specific strategy aimed at searching for published studies will be employed. A structured search of appropriate databases will be conducted, with subsequent analysis of title and abstract text words, as well as the index terms associated with each article. Identified keywords will then be entered into a second search within each database. Furthermore, the reference lists of all identified articles will be searched to identify additional studies.

This search will be limited to articles in English with no limitation regarding date of publication. The following databases will be utilized to conduct the search: CINAHL, MEDLINE, SPORTDISCUS, PUBMED, DynaMed, and the Joanna Briggs Institute Database of Systematic Reviews & Implementation Reports. All literature related to ER, regardless of date of publication, will be eligible for this review. No publication date limitation will be set as it is important to gain a detailed overview of treatment procedures, and examining the progression over time could likely yield informative results.

Initial keywords to be used will include: “rhabdomyolysis”, “exertional rhabdomyolysis”, “acute exertional rhabdomyolysis”, “AER”, “treatment”, “return to play”, “recognition”, “myoglobinuria”, “diagnosis”, “athletic training”, “sickle cell”, “sickle cell trait”, “athlete”, “athletic population”, “health provider(s)”, “fluid replacement”, “creatine kinase”, and “acclimatization”.

### **Assessment of methodological quality**

Papers selected for retrieval will be assessed by two independent reviewers for eligibility prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

### **Data collection**

Data will be extracted from the papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix 1). The data extracted will include specific details about the phenomena of interest, populations, study methods and outcomes of significance to the review question and specific objectives. Should data extraction not be possible from a literature source, the reviewers will attempt to contact the authors for clarification when possible.

### **Data synthesis**

Data will, where possible, be pooled using JBI-MAStARI. This will involve the aggregation or synthesis of conclusions to generate a set of statements that are representative of that aggregation, through assembling and categorizing these conclusions on the basis of similarity in meaning. These categories are then subjected to a meta-synthesis in order to produce a single comprehensive set of synthesized findings that can be used as a basis for evidence-based practice. The reviewers will determine which data can and should be combined by evaluating the homogeneity of results among the various studies. Where statistical pooling is not possible, the conclusions will be presented in narrative form. Case reports and opinion papers will undergo evaluation for homogeneity regarding patient outcomes of interest.

### **Conflicts of interest**

There are no conflicts of interest evident for this review.

### **Acknowledgements**

There are no acknowledgements the reviewers wish to make.

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## Appendix I: Appraisal instruments

### MAStARI appraisal checklist for descriptive/case series

#### JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer ..... Date .....

Author ..... Year ..... Record Number .....

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Were the criteria for inclusion in the sample clearly defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Were confounding factors identified and strategies to deal with them stated?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Were outcomes assessed using objective criteria?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. If comparisons are being made, was there sufficient descriptions of the groups?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Was follow up carried out over a sufficient time period?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Were the outcomes of people who withdrew described and included in the analysis?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Were outcomes measured in a reliable way?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Was appropriate statistical analysis used?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal:    Include                     Exclude                     Seek further info

Comments (Including reason for exclusion)

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## Appraisal Instruments

### MAStARI appraisal checklist for cohort/case control

#### JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer ..... Date .....

Author ..... Year ..... Record Number .....

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Are the patients at a similar point in the course of their condition/illness?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Has bias been minimised in relation to selection of cases and of controls?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Are confounding factors identified and strategies to deal with them stated?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Are outcomes assessed using objective criteria?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Was follow up carried out over a sufficient time period?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Were the outcomes of people who withdrew described and included in the analysis?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Were outcomes measured in a reliable way?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Was appropriate statistical analysis used?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal:    Include                   Exclude                   Seek further info.

Comments (Including reason for exclusion)

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