Clinical Practice Guidelines for Exertional Rhabdomyolysis: A Military Medicine Perspective

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Abstract

Exertional rhabdomyolysis (ER) is an uncommon condition with a paucity of evidence-based guidance for diagnosis, management, and return to duty or play. Recently, a clinical practice guideline for diagnosis and management of ER in warfighters was updated by a team of military and civilian physicians and researchers using current scientific literature and decades of experience within the military population. The revision concentrated on challenging and controversial clinical questions with applicability to providers in the military and those in the greater sports medicine community. Specific topics addressed: 1) diagnostic criteria for ER; 2) clinical decision making for outpatient versus inpatient treatment; 3) optimal strategies for inpatient management; 4) discharge criteria; 5) identification and assessment of warfighters/athletes at risk for recurrent ER; 6) an appropriate rehabilitative plan; and finally, 7) key clinical questions warranting future research.

Introduction

Exertional rhabdomyolysis (ER) is a relatively uncommon condition seen among warfighters and athletes (WA) which, in severe cases, can be life-threatening (1). During 2019, the U.S. military reported 512 incident cases of ER, for an unadjusted incidence rate of 38.9 cases per 100,000 person-years (2). Although the incidence among civilian athletes is likely similar to that in the military (perhaps higher, depending on the sport), the incidence among the general civilian population is likely much lower. A recent, 13-year retrospective cohort study in a U.S. civilian community showed one to two cases per 100,000 person-years (3). Many intrinsic and extrinsic factors are known to increase risk for ER (4,5). In most cases, individuals with ER are able to fully recover and safely return to duty or play (RTD/P) after identifying and mitigating any precipitating factors. However, a subset will experience persistent exercise intolerance, recurrent rhabdomyolysis, career-ending complications (*e.g.*, extensive lower extremity fasciotomies), or rarely, death (6,7). Clinicians treating patients with ER are confronted with challenging decisions including when outpatient versus inpatient management is appropriate, when the WA can safely RTD/P, and whether the WA require further testing for an underlying disorder.

In early 2020, a multidisciplinary team of physicians and scientists within the U.S. Department of Defense revised and updated a clinical practice guideline (CPG) (1) to assist providers in evaluating and managing warfighters with ER (https://www.hprc-online.org/resources-partners/whec/clinical-care/clinical-practice) (1). This CPG is based on published evidence, and where lacking, expert consensus opinion. The intent of this article is to introduce this CPG (1) to the greater military and sports medicine communities to highlight the military's approach to challenging clinical questions and particular areas of clinical controversy. As ER remains a clinical problem in the sports medicine community with limited evidence-based guidance, we conclude by identifying key unanswered questions that require further research.

What Is Exertional Rhabdomyolysis?

ER is pathologic skeletal muscle breakdown resulting from physical exertion which necessarily manifests with both clinical and laboratory findings. A diagnosis of ER is made when there are severe muscle symptoms (pain, stiffness, and/or weakness) and laboratory evidence of myonecrosis (creatine kinase [CK] level $\geq 5\times$ upper limit of normal [ULN]) in the setting of recent exercise (4,8,9). An

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1537-890X/2003/169–178
Current Sports Medicine Reports

algorithm for initial evaluation, diagnosis, and treatment of ER is presented in Figure 1.

ER typically occurs with activities or sports involving intense, prolonged, and/or repetitive muscle overload (especially eccentric loading, due to greater resultant muscle damage) (1,5). The intensity of the culpable physical exertion is often much greater than what the individual is accustomed. The concept of cumulative load is important to consider as well; the accumulated muscle damage incurred over the days prior to a particularly intense workout, with inadequate recovery, often sets the stage for the development of ER. This acute and cumulative overload results in local tissue hypoxia, failure of the ATP-dependent sodium-potassium and calcium ATPase pumps, and reliance on anaerobic glycolysis. This in turn leads to increased intracellular calcium, metabolic acidosis, sarcolemma permeability, and myocyte death (5,8,14).

Beyond severe muscle symptoms, the deleterious effects of ER may be mild to severe and potentially fatal. The outcome is the result of a complex interplay among mechanisms involving tissue damage, hypoperfusion, oxidation, and electrolyte disturbances. Severe cases of ER may exhibit:

- Acute compartment syndrome, because of fluid shifts into injured muscle tissues in response to large scale spillage of intracellular proteins and electrolytes;
- Acute tubular necrosis and renal failure, because of kidney hypoperfusion, metabolic acidosis, and myoglobin sludging in renal tubules;
- Disseminated intravascular coagulation, due to tissue damage releasing procoagulant factors;
- Cardiac dysrhythmia, due to electrolyte disturbances (5,9).

Numerous extrinsic and intrinsic factors have been described to increase risk of developing ER. Extrinsic factors are external to the body and its innate physiology, while intrinsic factors "come from within." These factors include:

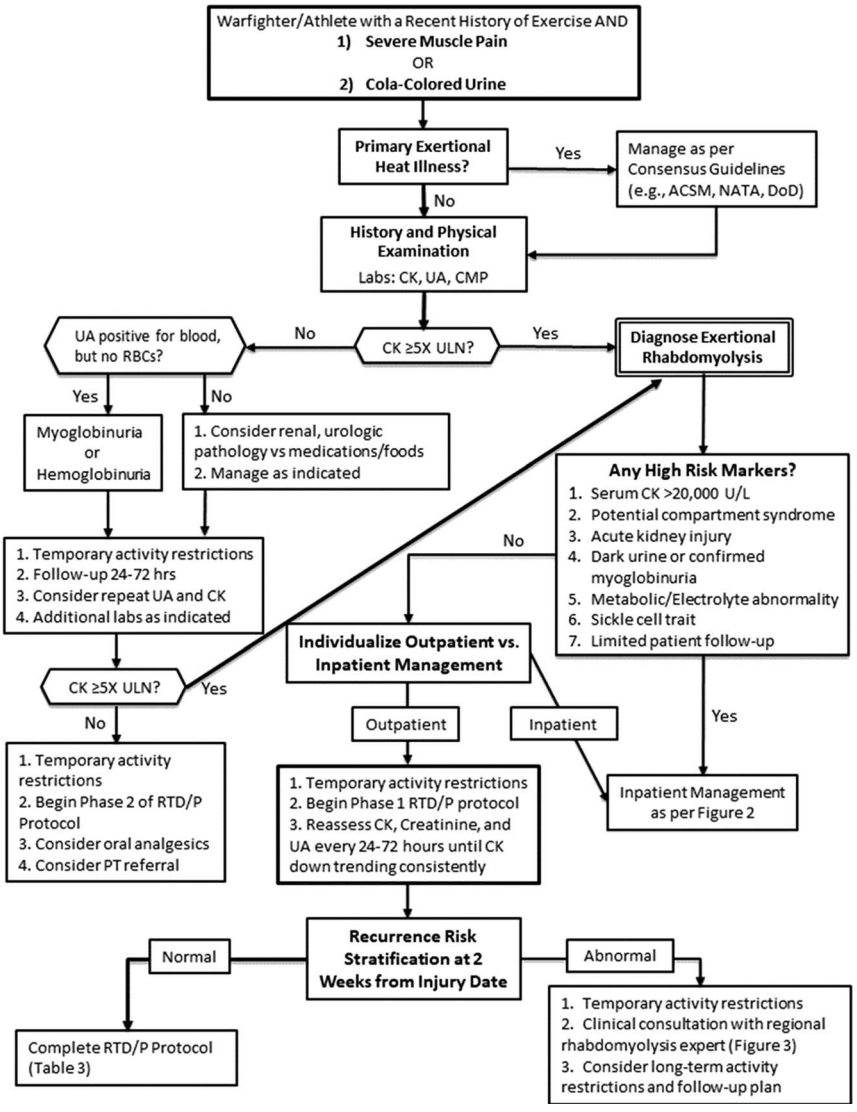

Figure 1: CPG for diagnosis and initial management of ER (9–13).

- Extrinsic:
  - Medications such as statins, amphetamines and other stimulants, antihistamines, antipsychotics, and alcohol (4,9,14)
  - Dietary supplements, especially those containing caffeine and other stimulants (15,16)
  - Extremes of environment (temperature, humidity, altitude) (5,14)
  - Leadership. The culture within an athletic department or military unit may be based on excessive emphasis on winning at all costs (and a misconception that more training/work will necessarily lead to better performance), leading to excessive risk tolerance or simply poor awareness of risks. This includes personnel at all echelons: athletic directors, head coaches, strength and conditioning staff, military commanders, and military training instructors (17).
- Intrinsic:
  - Medical conditions such as infection (18), dehydration (5,14,19), hypothermia and hyperthermia (14), and heat stroke (5)
  - Genetic, metabolic, or autoimmune disorders, often previously subclinical (such as glycogen storage diseases and disorders of lipid metabolism) (7)
  - Sickle cell trait (SCT) (5)
  - Deconditioned state (especially in the setting of rapidly accelerated physical training (20,21)
  - High motivation/drive to persist, such as military trainees and warfighters where perseverance through physical tasks is required (17)

By definition ER is symptomatic (severe muscle pain and/or stiffness) (1,5,7,14,22), and should not be confused with two other related, but distinct, exertion-related conditions:

- Delayed onset-muscle soreness (DOMS): DOMS is a self-limited physiological response to exercise resulting in mild-to-moderate myalgias and elevations in serum muscle enzyme levels; ER could be considered an extreme continuation of DOMS, (14,23) and DOMS as a symptom may exist with or without significant underlying pathology such as ER.
- *"HyperCKemia" (elevated serum CK without ER muscle symptoms):* Athletes exhibiting laboratory findings (*i.e.*, elevated CK and myoglobinuria) consistent with ER without the severe clinical muscle symptoms necessary for the diagnosis of ER; such patients, even with severely elevated CK levels, do not have ER and end organ damage has not occurred. It is well accepted that even low- to moderate-intensity exercise results in release of CK into the circulation in varying degrees with no clinical consequence (7,8,14,22).

What Biomarker(s) Should Be Used to Diagnose and Monitor ER?

When myocytes are overwhelmed by the demands of exercise, the muscle unit leaks its contents into the systemic circulation, consisting of intracellular electrolytes, metabolites, and proteins (aldolase, myoglobin, CK, lactate dehydrogenase, aspartate transaminase). Of these, myoglobin is the only protein unique to muscle, as a small subunit of CK can be found in the brain. Unfortunately, serum myoglobin is not a suitable biomarker for two reasons. First, myoglobin typically peaks in the serum around 3 h after exercise and returns to baseline within 6 to 24 h. Most patients with ER present 24 to 72 h after the offending activity, well after myoglobin has reached its peak. Second, many treatment facilities have difficulty producing timely laboratory results on serum or urine myoglobin. Therefore, total serum CK (not fractioned) is used as the current gold-standard biomarker for diagnosis and monitoring of ER. In addition to a serum CK, initial laboratory evaluation includes a comprehensive chemistry panel and urinalysis with microscopic examination. For biomarker monitoring purposes, the CK level often reaches its peak around 24 to 48 h after exercise, and then will decrease by approximately 50% every 48 h (24). Kidney function and electrolytes (including serum phosphate) should be monitored as well, regardless of management in an outpatient or an inpatient facility.

The CK ULN is defined by each laboratory, but is usually about 200 $U \cdot L^{-1}$. Baseline and physiologic post-exertion CK levels are quite variable, even among individuals. An individual's CK level also is influenced by age, gender, muscle mass, ethnicity, type of activity, as well as medical history (4,22,25). African American (AA) males typically have baseline CK levels twice those of Caucasian males, while AA females are 1.5 times higher than white females (26). Swimmers have been found to have post-exertion CK levels 3 times lower than soccer players (24). It also is not unusual to have resting CK levels of 600 to 700 in certain individuals already exceeding the ULN of normal in their pre-exercise state (25). In a prospective study of 499 Army recruits in basic training, the average CK level at day 7 was 1220 $U \cdot L^{-1}$ (range, 56 to 35,056 $U \cdot L^{-1}$, which exceeds 5× ULN; however, none had clinical symptoms consistent with ER or required any treatment for ER (22). Thus, elevated CK above baseline is a normal and variable response to exercise, and does not represent ER without overt signs and symptoms (4,8,9,22).

The widely accepted diagnostic threshold of CK ≥5× ULN is extremely sensitive but poorly specific. Multiple studies have shown that WA regularly reach a CK >5× ULN as a normal physiologic response to their respective activity. For example Hunkin et al. showed that elevated CK could be a sign to show incomplete recovery from previous training episodes (27). Although many sports are associated with increased CK levels (22,28–31) a few, including ultramarathon running and American football, have received particular attention. A study of division I collegiate American football players in preseason found CK levels rose substantially in the first week of preseason practice, from a baseline mean of 285 $U \cdot L^{-1}$ to a day 7 mean of 1,562 $U \cdot L^{-1}$ (32). Some organizations have established baselines by obtaining a pre-season CK level and then monitoring post-activity levels during the season (24). Some experts have recommended a diagnostic threshold of CK ≥50× ULN (approximately 10,000 $U \cdot L^{-1}$) among WA for increased specificity (22). However, normal values vary based on race, age, sex, body mass, fitness level, and sport/activity, but these norms have not been well defined nor implemented in laboratory reference standard ranges (22,26). Thus, in patients with severe muscle pain and tenderness, we

endorse a conservative diagnostic threshold of CK ≥5× ULN for general use to minimize false negative diagnoses, which may lead to a poor outcome. The timing of blood testing must be considered along with the diagnostic threshold, because a CK level taken within the first 12 to 24 h after injury will likely not have reached its peak, and will need to be repeated later to rule out ER (Fig. 1). Finally (and again), it must be remembered that ER is not diagnosed based on laboratory values alone, but on consistent clinical findings, including severe muscle symptoms (5,7).

What Is the Significance of an Athlete Presenting with Cola-Colored Urine or a Urinalysis Positive for Blood?

Dark or "cola-colored" urine in an athlete can be an early sign of ER or it can be caused by several other conditions, some serious and some trivial (14,33–35). Given this, dark urine in an athlete deserves prompt additional evaluation, beginning with a formal urinalysis with microscopy. In cases of ER, the urinalysis will be positive for blood, but no red blood cells (RBCs) will be seen on microscopy; this is presumptively due to myoglobinuria (17). Figure 1 shows that such WA should undergo additional lab testing to include a metabolic panel and CK level for assessing the level of myonecrosis. As described above, myoglobin levels often peak 12 to 24 h prior to those of CK, but because the half-life is only 2 to 3 h, levels often return to normal within 24 h after the onset of the injury (36). As such, laboratories should be repeated in 24 h to most accurately assess peak levels (36).

Other subtypes of patients may present with dark urine and a positive urinalysis for blood without RBCs on microscopy. For example, patients with a metabolic myopathy may present with dark urine and classically have little to no muscle pain. Although much less common than ER, the initial workup of these patients is very similar to those with ER (4). When metabolic myopathy is suspected, a neurologist (ideally with neuromuscular sub-specialty fellowship training) should be consulted for further evaluation and management. Finally, hematuria (RBCs in the urine) or hemoglobinuria may present in this fashion as well. While intense or prolonged exercise commonly results in low-grade hematuria or hemolysis, it can rarely lead to gross hematuria or hemoglobinuria with "cola-colored" urine.

Because the workup and treatment for hematuria and hemoglobinuria are very distinct from that of ER, we recommend that any dark urine sample positive for blood should be spun, as dark or red urine sediment indicates hematuria from glomerular, non-glomerular, and/or urologic causes. In these cases, and those where microscopy show elevated RBC levels, the urinalysis should be repeated and the patient managed in collaboration with a nephrologist or urologist, depending on the etiology. On the other hand, when the urine supernatant (top, liquid portion of a spun urine sample) is red or dark with no RBCs in the sediment, the most common causes are myoglobinuria (consistent with ER), hemoglobinuria (due to hemolysis, such as exercise-induced hemolysis), urine discoloration from medications or foods, or rarely, porphyria (17,33,34). The bottom line is that any athlete presenting with dark or "cola-colored" urine deserves immediate further workup and that this workup begins with a carefully examined urinalysis with microscopy.

How Should an Athlete Be Stratified for Inpatient versus Outpatient Treatment?

Typically, ER can be safely and effectively treated as an outpatient, which is both cost-effective and generally preferred by patients. Determining which patient requires inpatient management is a critical decision point and should be individualized. This decision should be based on specific factors known to increase the likelihood of medical complications and/or mortality (Table 1). Patients with one or more high-risk markers should be strongly considered for inpatient management. Because many biomarkers will trend upward in the early course of ER, there is an element of uncertainty when triaging for inpatient versus outpatient care. However, when certain labs (*e.g.*, creatinine, phosphate) are elevated initially, it is anticipated that the patient will not succeed in the outpatient setting.

Acute kidney injury (AKI) is a common and often serious complication of ER. Admission is warranted when labs show AKI, which is defined by Kidney Disease: Improving Global Outcomes criteria as any of the following: 1) an increase of serum creatinine by ≥0.3 $mg \cdot dL^{-1}$ (≥26.5 $\mu mol \cdot L^{-1}$) within 48 h; 2) a serum creatinine ≥1.5 times baseline level within previous 7 d; 3) urine output of <0.5 $mL \cdot kg^{-1} \cdot h^{-1}$ for 6 to 12 h (37). Any ER patient with preexisting kidney disease also should receive inpatient management. McMahon et al. (38) derived a clinical prediction tool for the risk of AKI with all-cause rhabdomyolysis. Although this calculator appears to be applicable to ER, it is worth noting that only 2.6% of the cohort studied (62 of 2371) had rhabdomyolysis due to exercise (38). No risk prediction scores are currently specific to ER.

Hypocalcemia and hyperphosphatemia deserve particular attention because both correlate with ER severity. Inpatient management is warranted when either of these conditions is present. Hyperphosphatemia is especially important because not only is it an indicator of disease severity, but it also may directly cause nephrotoxicity (termed acute phosphate nephropathy), especially when persistent and/or greater than 5.4 $mg \cdot dL^{-1}$ (39,40).

Although the mechanism is unknown, ER is more common and more likely to be severe among those with sickle cell trait (SCT) (41). In WA with SCT, severity of the myonecrosis often reaches a fulminant level very quickly, even "explosively." This syndrome often presents as a conscious collapse during

Table 1.
High-risk factors suggesting inpatient management for ER is indicated.

CK > 20,000 $U \cdot L^{-1}$
Potential compartment syndrome
Acute kidney injury (serum creatinine increase of ≥0.3 $mg \cdot dL^{-1}$ within 48 h, OR
serum creatinine 1.5 times baseline level within previous 7 d, OR a urine output of <0.5 $mL \cdot kg^{-1} \cdot h^{-1}$ for 6 to 12 h) (27)
Dark urine or confirmed myoglobinuria
Metabolic abnormality (*e.g.*, hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, acidosis)
Sickle cell trait carrier
Limited patient follow-up

exercise, and is termed exertional collapse associated with sickle cell trait (ECAST) (42,43). In cases of ER complicated by SCT (especially with ECAST), there is an increased risk of compartment syndrome, electrolyte/metabolic disturbances, arrhythmias, and sudden death. In fact, one leading researcher posited that ER appears to never cause fatality in the absence of SCT or exertional sickling (44). All patients with SCT who present with ER should be managed as inpatients. In the absence of any high-risk factors (Table 1), ER outpatients are both safely and effectively managed with oral hydration and frequent follow up.

What Is the Optimal Inpatient Management of ER and Any Associated Complications?

On admission, the general goals of management are to prevent and/or manage AKI by protecting the kidneys from the nephrotoxic effects of myoglobin, monitoring for compartment syndrome, and mitigating potential complications such as metabolic acidosis and/or electrolyte abnormalities. Figure 2 presents an algorithm for inpatient management of ER.

Renoprotection

Intravenous (IV) fluids are administered to maintain adequate urine output and decrease the nephrotoxic effects of myoglobin. It is important to recognize that IV fluids are for renoprotection and not necessarily for hydration. Understanding this concept is critical in determining the rate and type of infusion and monitoring for AKI. However, data on optimal fluid type and rate are limited. One small, randomized, controlled trial of non-ER patients found significantly higher blood and urine pH and a trend toward faster normalizing of CK to <200 $IU \cdot L^{-1}$ when using Lactated Ringer's solution (LR) compared to normal saline (NS) at a flow rate of 400 $mL \cdot h^{-1}$ (45). In this study, all patients receiving NS required 140 (100 to 700) mEq of sodium bicarbonate for urine alkalization ($P < 0.001$), whereas only 2 of 15 in the LR group received sodium bicarbonate (45). In our experience, there is little difference between LR and NS for treating ER, but these limited data suggest LR may lessen the need for sodium bicarbonate. Systematic reviews of studies reporting an initial fluid rate noted rates ranging from 200 to 1000 $mL \cdot h^{-1}$, with maintenance rates from 120 to 300 $mL \cdot h^{-1}$. No correlation has been found between type of fluid and decreased length of stay (46,47). Another systematic review found several studies that targeted 300 ml or more of urine output (48). Overall, we recommend IV fluids be given at initial rates of 400 to 1000 $mL \cdot h^{-1}$ to establish adequate urine output (Fig. 2), then titrated down to

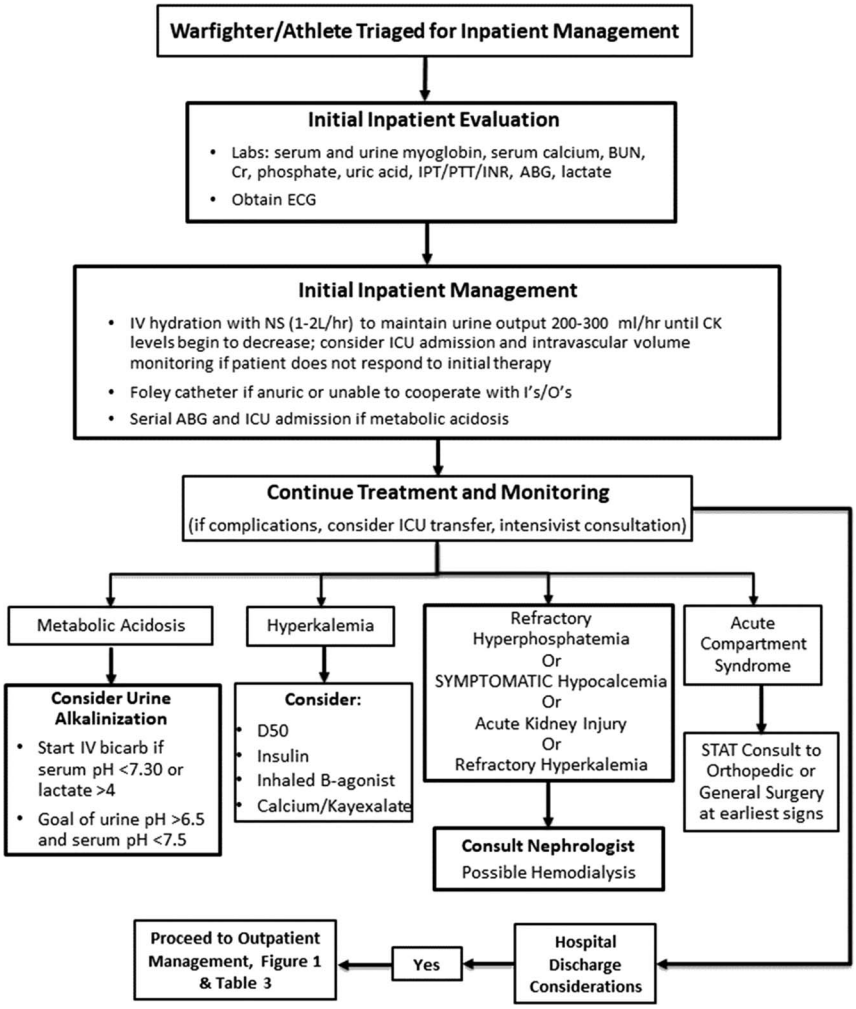

Figure 2: Inpatient Management of Acute ER.

200 to 300 mL·h^{-1} to maintain a balance between fluid input and output. If NS is selected, once urine output is established, we recommend switching to LR or ½ normal saline to avoid hypernatremia and hyperchloremia. The specific role of urine alkalinization remains controversial, but likely should be considered for renoprotection and management of metabolic acidosis, especially if urine pH remains <6.5 (49). In our experience, ER without AKI responds well to NS or LR without alkalinization of the urine. When proceeding with alkalinization, the target urine pH is >6.5 while maintaining serum pH < 7.5. This can be accomplished by adding two ampules of sodium bicarbonate to 1 L of D5W, and administering intravenously at a rate of 75 to 125 mL·h^{-1}. Simultaneously, NS or LR can be given through a second IV to achieve a total rate of 200 to 300 mL·h^{-1}. While fluids containing bicarbonate are running, monitor serum potassium, calcium, and urine pH every 4 h. It should be remembered that alkalinization can worsen hypocalcemia. Consider nephrology consultation if serum calcium drops or urine pH does not rise.

Monitor for Complications

During the hospital course, CK levels should be monitored every 12 h to ensure muscle recovery is occurring, but this interval should be shortened if clinical concerns exist (*e.g.,* increasing pain, signs of compartment syndrome). Once a downward CK trend is established, the testing interval can be progressively lengthened as the patient stabilizes. It is important to note that IV fluids are for renoprotection and, depending on the time course of admission, CK could be rising, declining, or changing minimally, despite adequate urine output. In general, during the initial hospitalization, CK monitoring should inform management. For example, a rising CK level despite adequate urine output may be normal early in the course. CK generally peaks anywhere from 2 to 7 d after the inciting event (31,50). No evidence suggests that increasing rate of IV fluids will lead to faster clearance of CK or necessarily improve outcomes. Furthermore, CK itself is not nephrotoxic, but rather serves as a marker of muscle damage and, to some degree, the process of muscle recovery. Pain may be maximal with peak CK and can be a good indicator to monitor during hospitalization. Pain may be controlled with acetaminophen, but non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided due to potential nephrotoxic effects.

Compartment syndrome is a rare but serious complication of ER (51,52). Frequent daily checks for pain out of proportion, adequate pulses, and neurologic function are recommended, depending on the major muscle groups affected. Any concern for compartment syndrome should prompt compartment pressure measurement and, if elevated, consultation with orthopedics for fasciotomy consideration (5,14).

Monitoring of electrolytes can help guide therapy. Clinicians should monitor and treat hyperkalemia, but, generally, asymptomatic hypocalcemia and hyperphosphatemia do not require treatment. Any treatment not responsive to IV fluids or associated with worsening kidney function should prompt consultation with nephrology.

When Can an Admitted Patient Be Safely Discharged?

There are no established "safe" discharge criteria with regard to specific values for CK or for ER in particular. Two retrospective reviews of 30 and 41 cases found discharge CK values ranging from 1410 to 94,665 U·L^{-1} and 10 to 61,617 U·L^{-1}, respectively (53,54). Neither report found any evidence for higher CK levels being associated with higher rates of re-admission. Generally, we recommend that clinicians consider discharge when CK downtrends and continues to downtrend in the absence of IV fluids. Demonstration of consistently downward trending CK, without IV fluids, indicates that CK will continue to decline.

Other factors important for safe discharge are improving renal function and reliable patient follow-up. Upon discharge, if CK remains >5000 U·L^{-1}, patients should be instructed to maintain fluid intake at about 1 liter per 6 h, with no more than 4 liters per 24 hrs. Patients also should monitor urine output to ensure adequate urine flow. Follow-up should occur within 48 to 72 h after discharge and CK should be re-evaluated to ensure continued improvement.

How to Identify WA with High Risk of Recurrent ER?

The majority of athletes with ER recover without any long-term sequelae or increased risk of recurrence (5,6). Some WA may have a high risk of recurrence and will need further testing and workup before safely returning to duty/play/activity. This testing may be quite extensive and complex, and in some cases, no specific diagnosis is reached. Thus, appropriate subspecialist consultation should be obtained (*e.g.,* neurologist with neuromuscular fellowship training) to assist with proper ordering and interpretation of these tests. Currently, no evidence-based guidelines delineate those WA who may be at high risk for recurrence, and we are currently actively researching this question. The following information represents consensus opinion for those WA considered to be at high risk for recurrence and warrant further evaluation prior to returning to duty.

Any WA who develops ER after a low-to-moderate workload should undergo further workup before clearance for RTD/P. Similarly, an athlete who does not clinically recover (normal exam and symptoms resolution) within 1 wk of proper rest and activity restriction also is at high risk for recurrence. Certain medications — statins, antipsychotics (*e.g.,* haloperidol) (41); stimulants (*e.g.,* amphetamines, methylphenidate) (55); and stimulant supplements (*e.g.,* caffeine, synephrine, octopamine, yohimbine, ephedra) (4) — can increase the risk of developing ER and therefore a chance of subsequent ER episodes. As a modifiable risk factor, further education and counseling regarding supplement use as well as medication adjustment would be necessary before RTD/P. For a list of other stimulants in supplements, see: https://www.opss.org/article/stimulants-dietary-supplements.

Laboratory findings associated with a higher risk of recurrence of ER include a CK peak of >100,000 U·L^{-1}, persistence of CK elevation >1000 U·L^{-1} despite rest for at least 2 wk, and ER complicated by AKI that does not return to baseline within 2 wk (5). Several personal or family medical conditions place individuals at high risk for recurrent ER, and any WA with such conditions should undergo further workup and testing. The workup should include gathering information regarding a personal or family history of previous ER, malignant hyperthermia, unexplained complications or death following general anesthesia, recurrent muscle cramps or severe muscle pain that interferes with activities of daily living, significant heat injury, or sickle cell trait or disease (5,7,41). In addition to the above, the WA must be defined as "low-risk" for recurrence before concluding a further workup can be deferred. To define a WA as low risk, he/she must have no high-risk criteria

and meet one of the following conditions: 1) a history of intense training; 2) known participation in an extreme conditioning program prior to developing ER; 3) ER in a group of individuals performing the same training or exertion; 4) an identifiable period of sleep and/or nutritional depletion; 5) a concomitant viral illness or other infectious disease; 6) taking a medication, anabolic steroid, or dietary ingredient previously associated with ER; or 7) having had excessive alcohol the night before.

What Further Testing Is Needed for WA Identified as High Risk?

If any one of the high-risk criteria is met or if the WA cannot be considered low risk for recurrence of ER, further evaluation is needed before RTD/P. Figure 3 presents our recommended algorithm for how testing and referrals may be done. Further management and potential evaluation for an underlying disorder may be determined in consultation with an appropriate specialist (often a neurologist with neuromuscular subspecialty training), and ideally such cases would be reviewed by a multidisciplinary panel. These subspecialists will assist in obtaining and interpreting appropriate diagnostic tests, and then facilitating corresponding treatment. The evaluation may include, but is not limited to electromyography (EMG), muscle biopsy, caffeine-halothane contracture test, genomic/proteomic testing, and/or exercise challenges. Muscle biopsy and EMG should be performed no sooner than 6 wk after rhabdomyolysis. Premature return to activity and post-ER acquired myopathy must be considered as potential causes of recurrent ER (56).

Metabolic myopathies are rare and may result from a variety of distinct etiologies but must be considered when the patient presents with cola-colored urine due to myoglobinuria after a low-to-moderate workload. The most common (or "least rare") etiologies are myophosphorylase deficiency (McArdle's disease — a glycogen storage disorder) and carnitine palmitoyltransferase II deficiency (CPT2 deficiency — a lipid metabolism disorder) (7). If a metabolic myopathy is suspected, laboratory evaluation should include serum lactic acid, plasma amino acids (to include carnitine), plasma acylcarnitine profile for evaluating disorders of fatty acid oxidation and organic acid metabolism, and urine organic acids (7,57). Additional evaluations may involve muscle biopsy and EMG, which should be performed at least 6 wk after rhabdomyolysis.

The following advanced tests should be ordered by an appropriate subspecialist who has been trained in the interpretation and differential diagnosis associated with possible findings. The Exercise Intolerance Panel is a blood test which can be used to determine presence of gene mutations or variants associated with increased susceptibility to ER (Table 2) (58). A Myoglobinuria Test Panel (MTP) is used to evaluate individuals who present with exercise intolerance-related weakness, pain, cramping, and idiopathic myoglobinuria. MTP tests for deficiencies in enzymes related to metabolic function and helps to specify the metabolic abnormality related to a specific disease (Table 2). The MTP is best performed in conjunction with a standard muscle biopsy to

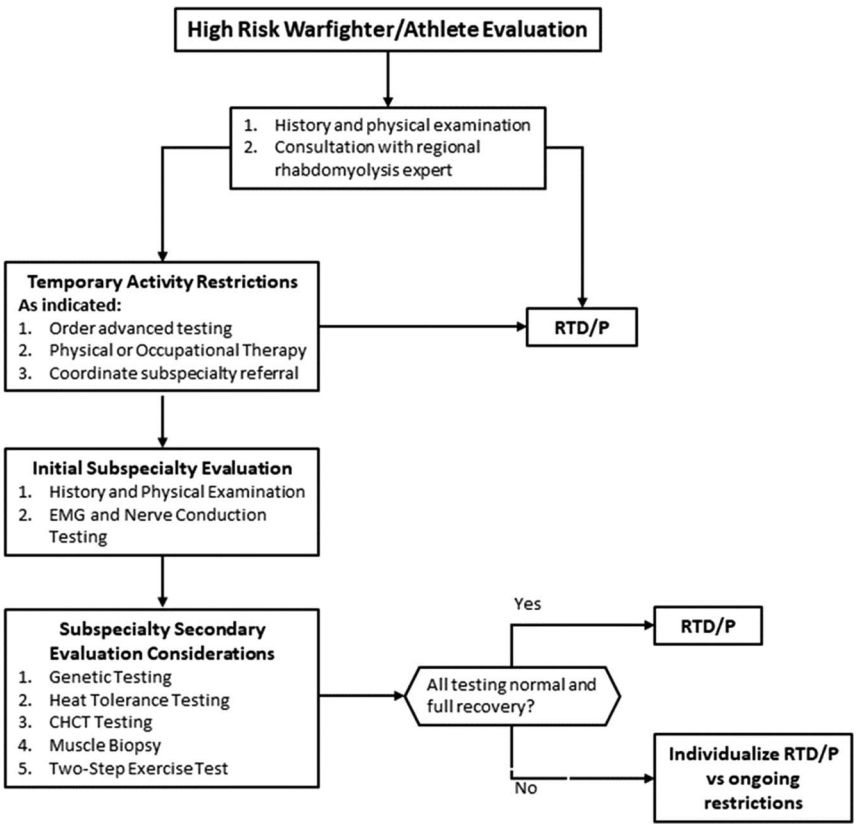

Figure 3: Evaluation of WA with features suggesting high risk of recurrent ER.

Table 2.
Advanced testing to identify conditions at high risk for recurrent ER.

Exercise Intolerance Panel	Carnitine Palmitoyltransferase II Deficiency
	→ CPT2 Gene: S113L, 413delAG, P50H, R503C, G549D, R631C
	Myophosphorylase Deficiency (McArdle's disease)
	→ PYGM Gene: R49X, G204S
	Myoadenylate Deaminase Deficiency
	→ AMPD1 Gene: Q12X, P48L
Muscle Metabolic Panel	Phosphofructokinase deficiency (PFK)
	McArdle's disease
	Tarui's disease
	Phosphoglycerate Kinase deficiency (PGK)
	Phosphoglycerate mutase deficiency (PGAM)
	Lactate Dehydrogenase deficiency (LDH)
	Glycogen, Phosphorylase A + Total deficiency (Ph)
	Phosphorylase B kinase deficiency (PhK)
	Carnitine Palmitoyltransferase 2 deficiency (CPT2)
	Myoadenylate Deaminase deficiency (MAD)

include frozen sections with full histochemistry (58). The Caffeine-Halothane Contracture Testing (CHCT) uses tissue from a muscle biopsy specimen to test for malignant hyperthermia (MH). The CHCT involves exposing *in vitro* muscle samples to increasing concentrations of caffeine and to halothane and then observing for increases in baseline and twitch contraction tension. A number of studies have investigated the possible link between ER and MH susceptibility (59–63).

Although currently primarily used as a clinical research tool, a two-step exercise test can evaluate for an abnormal increase in CK related to exercise. The test includes stepping up and down two stairs of 30 cm height each for 5 min at a set pace (54 steps per minute using a metronome). Then the individual performs 15 double-leg squats in 1 min (3 s down, 2 s up). Participants wear a backpack weighted at 30% of bodyweight during the tests. Blood samples are taken before, immediately after, and 48 and 72 h after completing the exercise. An exercise-induced increase in CK from baseline of >230 $U \cdot L^{-1}$ categorizes participants as a high CK responder (64). The underlying principle with the two-step test is most important: a standard exercise load is administered, followed by CK levels drawn at specific time intervals.

When Can an Athlete with ER Safely Return to Play?

Once WA have no clinical symptoms (weakness, swelling, pain, soreness), a CK level <5× ULN, and a normal UA, they can be considered for RTD/P (6,65). Evidenced-based guidance to assist providers in returning a WA to unrestricted activity is limited, but expert consensus guidelines have been proposed (1,6) and validated by a study of 10 collegiate football players (66). We also propose a four-phase program as a construct to safely return low-risk WA to duty/sport while concomitantly minimizing risk of ER recurrence (Table 3). Phase 1 lasts a minimum of 72 h and focuses on significant activity modification and early follow-up. WA are encouraged to rest or perform light activity indoors, get 7 to 8 h of sleep per night, drink plenty of fluids, and increase their sodium intake through foods (*e.g.*, cottage cheese, peanuts/nuts, pretzels, soy sauce, canned salmon, canned beans). Resistance training should be avoided until phase 2, and then added progressively as noted below. Progression to phase 2 is dependent on the outcome of repeat laboratory findings for CK and lack of clinical symptoms. CK and UA analyses should be repeated 72 h after the last known test. If the results are <5× ULN, UA continues to be normal, and the WA remains symptom free, then phase 2 may begin (6). Otherwise, the WA should be considered for inpatient versus outpatient management, evaluated for high-risk markers, and remain in phase 1 with follow-up CK/UA every 72 h until the

Table 3.
Phased approach to RTD/P for WA diagnosed with ER.

Phase 1:
• Light indoor duty for 72 h, encourage oral hydration and increased salt intake
• Avoid resistance training
• Sleep 7–8 consecutive hours nightly
• Follow-up in 72 h for repeat CK/UA
• If CK value is <5× ULN and UA continues to be normal, phase 2 may begin
• If CK is ≥5× ULN or the UA is positive for blood with no RBCs the athlete should be considered for high-risk markers, inpatient versus outpatient management, and remain in phase 1 with follow-up every 72 h for repeat CK/UA until the above criteria are met
• If CK remains ≥5× ULN and/or the UA is persistently abnormal for 2 wk after injury, refer for expert consultation
Phase 2:
• Begin light outdoor activity, no strenuous physical activities
• Begin lightweight resistance training (bodyweight or 20%–25% 1RM)
• Supervised (physical therapy, athletic training, etc.) physical activity at own pace and distance
• Follow up with provider in 1 wk
• If no clinical symptoms, begin phase 3. Otherwise remain in phase 2 and return at 1-wk intervals.
• Progress to phase 3 when there is no significant muscle weakness, swelling, pain, or soreness
Phase 3:
• Increase resistance exercise to 50%–75% of 1RM
• Add or increase agility drills at 70%–80% of maximal effort
• Add or increase running to 50%–70% of normal time or distance
• Progress to phase 4 if no significant clinical symptoms
Phase 4:
• Return to full participation
• Follow-up with provider as needed

above criteria are met (6). Phase 2 introduces light outdoor, but no strenuous activities, and lightweight resistance training (body weight training or 20% to 25% of 1 repetition max [1RM]) (66). These activities should, if possible, be supervised by a physical therapist or athletic trainer. The WA should follow up with a provider after 1 wk, and may progress to phase 3 if clinical symptoms are absent. If clinical symptoms return, the WA should remain in phase 2 with weekly follow-ups until activities can be completed symptom-free. Phase 3 increases the intensity of exercise: resistance training can be performed at 50% to 75% of 1RM, agility drills at 70% to 80% of maximal effort, and running can begin at 50% to 75% of normal time and distance (66). Finally, phase 4 returns the WA to full physical training with follow up as needed. Because muscle pain serves as a clinical guide for progression through the phases, pain relievers (acetaminophen and NSAIDs) should be used sparingly so as to not mask pain.

Unanswered Clinical Questions

Although ER is largely preventable and much progress has been made with its diagnosis and management, it remains a challenging problem. Incidence rates have continued to rise, including reports of case clusters, or "team rhabdomyolysis" (17,44). Multiple important clinical questions pertaining to ER remain unanswered. Some of these include:

- How should high risk factors be weighted to create a risk stratification algorithm?
- What genes and what patterns of gene expression predict risk of ER?
- What combinations of medications and supplements are triggers for ER?
- Can risk of AKI be accurately predicted in the early course of ER, and if so, how?
- What is the mechanism by which SCT increases risk for ER?
- Is the ER of ECAST fundamentally different than ER in someone without SCT?
- What is the optimal stepwise evaluation for individuals at high risk for recurrent ER?
- What local and regional variations exist in clinical practice with respect to ER diagnosis and management? To what extent are these variations related to poor medical education?

All deserve to be studied; some are currently being addressed by ongoing research studies. Achieving a sustained reduction in incidence with improved of outcomes hinges upon finding the answers to these and other questions.

Conclusions

ER continues to occur among individuals, such as warfighters and athletes. Backed by published evidence and expert consensus informed by decades of experience in treating warfighters with ER, we offer this CPG as an approach for effectively evaluating and managing warfighters and athletes with ER.

The authors would like to recognize and acknowledge the work of Dr. Yuval Heled, prior director of the Israeli Defense Force's Heller Institute, as well as Drs. Eric Marks (Internal Medicine), Glen Cook (Internal Medicine), and John Baron (Nephrology) in formulating the early construct of this Department of Defense ER CPG with the senior authors, FO and PD. Additionally, the authors would like to thank Dr. Ian Stewart (Nephrology) for his expert consultation in the most recent revision of the DoD ER CPG.

The authors declare no conflict of interest and do not have any financial disclosures.

This project was completed without grants; however, Department of Defense equipment and facilities were used in writing.

The opinions herein are those of the authors. They do not represent official policy of the Department of Defense or any of its components.

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