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Clinical Practice Guideline for the Management of **Exertional Rhabdomyolysis** in Warfighters

A Collaborative Effort of United States Military Joint Service Medical Providers

In conjunction with
The Army Heat Center and the
Consortium for Health and
Military Performance (CHAMP)
Warrior Heat- and Exertion-
Related Events Collaborative (WHEC)

The Army Heat Center at Fort Benning

CHAMP Uniformed Services University

WHEC WARRIOR HEAT- AND EXERTION-RELATED EVENTS COLLABORATIVE

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SECTION 1: EXECUTIVE SUMMARY

Definition. A diagnosis of exertional rhabdomyolysis (ER) is made when there are severe muscle symptoms (pain, stiffness, and/or weakness) AND laboratory evidence of myonecrosis with a creatine kinase (CK) level ≥5,000 IU/L in the setting of a proximate significant exercise history.

Contributing Factors. High-intensity, repetitive, or prolonged unaccustomed exercise unmatched to fitness level; excessively motivated individual; inexperienced trainers and/or leaders; medications or dietary supplement use (especially stimulants); hot and humid climate; genetic factors (sickle cell trait, disorders of lipid or glycogen metabolism, etc.); recent viral illness; sleep deprivation; and pre-exercise/activity hypovolemia.

Inpatient Admission. Decision to admit must be individualized. Those with any high-risk criteria should be strongly considered for admission.

High-risk criteria for admission consideration:

- CK ≥20,000 IU/L
- Suspicion for potential compartment syndrome
- McMahon Score ≥6
- Laboratory evidence of acute kidney injury (AKI)
- Dark urine or confirmed myoglobinuria
- Metabolic abnormality (e.g., hyperkalemia, hyperphosphatemia, acidosis)
- Sickle cell trait (SCT) carrier
- Unreliable patient follow-up (e.g., Warfighter lives alone, unit in field-exercise training)

Outpatient Treatment Criteria. ER patients in the absence of high-risk criteria (see above) generally may be treated as outpatients. Outpatient treatment in such patients consists of oral fluid intake, limited physical activity, and close follow-up (often every 24 to 72 hours in early stages).

Inpatient Discharge Considerations. After admission and appropriate treatment, discharge may be considered after demonstrating downtrending CK, improving symptoms, improving or resolved AKI and metabolic abnormalities, and a reliable plan for continued follow-up.

High-risk Markers for Recurrence Risk Stratification

- Delayed clinical recovery (despite more than 1–2 weeks of activity restriction)
- Persistent CK elevation >1,000 IU/L, or sex- and/or race-specific 95th percentile, despite rest for at least 1–2 weeks
- ER complicated by AKI with a creatinine that does not return to baseline in 2 weeks
- ER after low to moderate workload
- ER complicated by drug or dietary supplement use (where the offending agent cannot be removed)
- CK peak >100,000 IU/L
- Personal or family history of ER, recurrent muscle cramps or severe muscle pain, sickle cell trait, malignant hyperthermia, unexplained complications, or family history of death following general anesthesia

Additional Guidance for Clinicians

- Serum CK is the "gold standard" for diagnosis and monitoring of ER; serum myoglobin is best used for risk prediction.
- Normal baseline and post-exercise CK levels vary by age, sex, race, and/or type of exercise.
- Recent consensus recommends a diagnostic threshold for ER in physically active people of CK >50× upper limits of normal (ULN; 10,000 IU/L) to improve specificity. This military-specific CPG update endorses a CK ≥5,000 IU/L in conjunction with an appropriate clinical history to diagnose ER in a Warfighter.
- Obtain and document a detailed history of supplement use in all cases of ER.

A Glossary with many of the terms used in this CPG is included as Section 7.

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SECTION 3: INTRODUCTION

Exertional rhabdomyolysis (ER) is a medical condition frequently observed in the setting of military training and operations. ER often occurs when the level of exertional stress is greater than the Warfighter is accustomed to.[1] This condition is commonly precipitated by several factors, often working in combination, which are further identified and described in this clinical practice guideline (CPG). A critical point for the military medical clinician to understand is that rhabdomyolysis is a medical term that broadly describes the phenomenon of skeletal-muscle breakdown with release of intracellular contents into the systemic circulation.[2] The etiology of rhabdomyolysis can be both complex and multifactorial; Table 1 identifies inherited and acquired etiologies. Rhabdomyolysis associated with inherited conditions is often triggered by the acquired conditions listed.

Table 1. Inherited and Acquired Etiologies of Rhabdomyolysis[2]

Inherited (Genetic Susceptibility)	Acquired (Triggers)
Glycolytic/glycogenolytic (e.g., McArdle disease [myophosphorylase deficiency])	**Exertion** (e.g., exercise, status epilepticus, delirium, electrical shock, status asthmaticus)
Fatty acid oxidation (e.g., carnitine palmitoyltransferase II deficiency)	**Crush trauma** (e.g., external weight, prolonged immobility, bariatric surgery, cardiopulmonary resuscitation)
Krebs cycle (e.g., aconitase deficiency)	**Ischemia** (e.g., arterial occlusion, compartment syndrome, sickle cell disease, disseminated intravascular coagulation)
Pentose phosphate pathway (e.g., glucose-6-phosphate dehydrogenase deficiency)	**Extremes of body temperature** (e.g., fever, exertional heatstroke, burns, malignant hyperthermia, hypothermia, lightning)
Purine nucleotide cycle (e.g., myoadenylate deaminase deficiency)	**Metabolic** (e.g., hypokalemia, hypernatremia or hyponatremia, hypophosphatemia, pancreatitis, diabetic ketoacidosis, renal tubular acidosis, hyperthyroidism or hypothyroidism, nonketotic hyperosmolar states)
Mitochondrial respiratory chain (e.g., succinate dehydrogenase deficiency)	**Drugs, supplements, or toxins** (e.g., anticholinergics, amphetamines, antihistamines, antidepressants, arsenic, ethanol, opiates, statins, cocaine, succinylcholine, halothane, corticosteroids, cyclosporine, itraconazole, phenothiazines, bath salts, synthetic cannabinoids)
Malignant hyperthermia susceptibility (e.g., familial malignant hyperthermia [RYR1] mutations)	**Infections** (e.g., Epstein-Barr virus, human immunodeficiency virus, herpes simplex, influenza A and B, *Borrelia burgdorferi*, tetanus, COVID)
Other (e.g., familial recurrent myoglobinuria, myotonic dystrophy, Duchenne and Becker muscular dystrophies)	**Inflammatory and autoimmune disorders** (e.g., polymyositis, dermatomyositis)

Importantly, while ER in Warfighters is more commonly identified during the summer months,[3-5] clinicians must be vigilant to recognize the distinction between rhabdomyolysis secondary to exertion (ER) and rhabdomyolysis as an end organ injury from exertional heat illness (EHI).[2] While ER can occur more frequently in the heat secondary to the increase in the relative workload, EHI may also result, but with a distinct clinical presentation. EHI often co-exists with secondary rhabdomyolysis and in one study was associated with 60% of the hospitalized cases of ER in U.S. Service Members.[6] The proper identification of rhabdomyolysis as either primary ER or secondary to EHI is not only clinically important, but imperative operationally with second-order effects on military profiling and return-to-duty decisions. These distinctions can be challenging for clinicians; discussion or consultation with clinicians experienced with heat-related illnesses and ER is advised.

In April 2024, the *Medical Surveillance Monthly Reports (MSMR)* reviewed the five-year surveillance period of 2019 to 2023. During this time the unadjusted incidence rates of ER per 100,000 person-years among U.S. active-component Service Members fluctuated, reaching a low of 38.0 cases in 2020 and peaking at 40.5 cases in 2023. Beginning in 2020, incidence rates per 100,000 person-years gradually increased, by 1.8% in 2021 (38.7 cases), 5.3% in 2022 (40.0 cases), and 6.6% in 2023 (40.5 cases). Consistent with prior reports, subgroup-specific crude rates in 2023 were highest among men less than 20 years old, non-Hispanic black Service Members, Marine Corps or Army members, and those in combat-specific and "other" occupations. Recruits experienced the highest rates of ER during each year, with incidence rates 6 to 10 times greater than all other Service Members.[1]

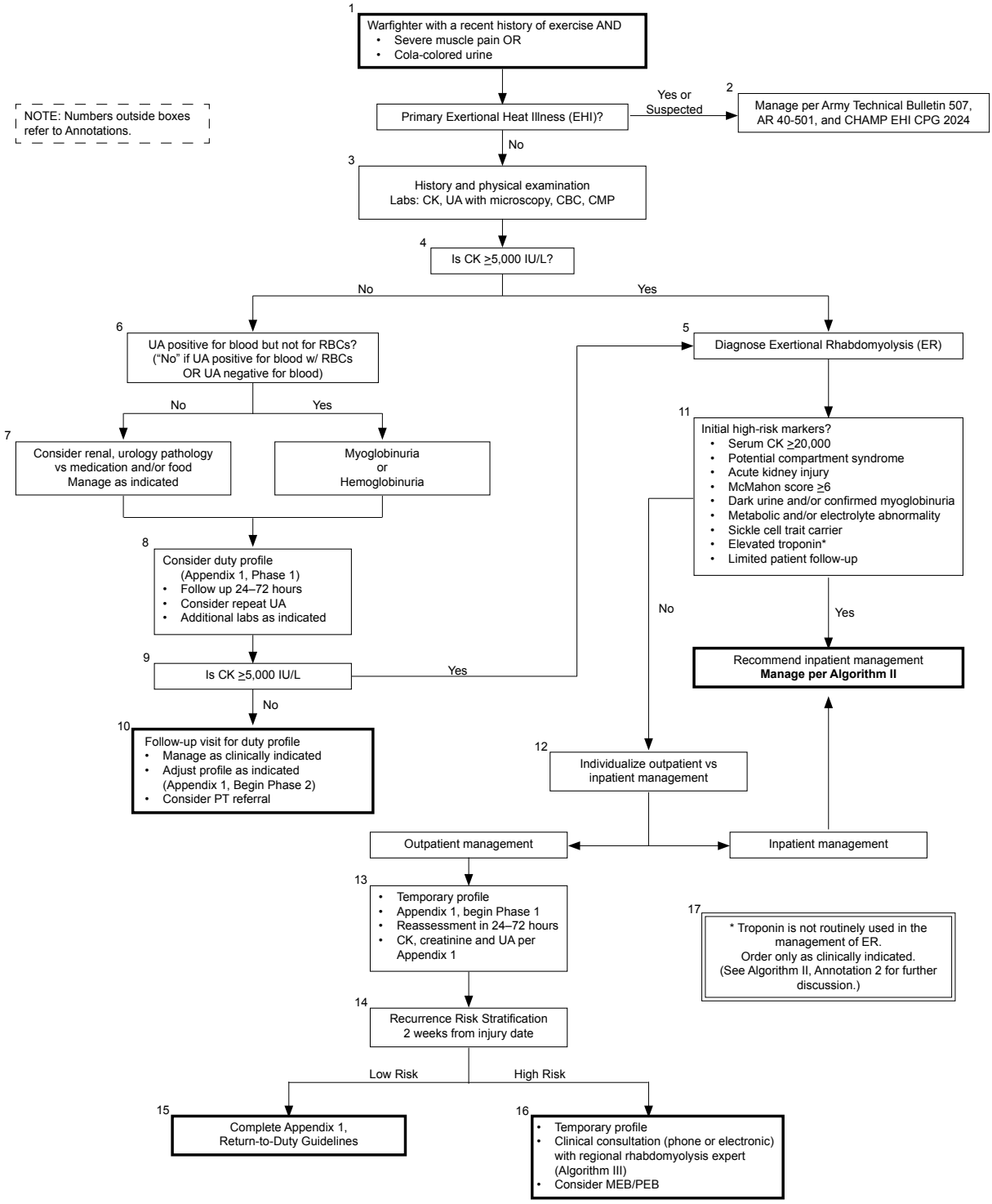
Although most Warfighters who experience ER recover and will be safely returned to duty, some may experience significant acute kidney injury (AKI) and/or muscular injury, while others may be identified as at risk for future recurrence. AKI may place the Warfighter at risk for future chronic kidney disease (CKD), while some muscular injuries may result in persistent functional deficits. In addition, recurrence may limit the Warfighter's effectiveness and potentially predispose them to future serious injury, including permanent disability, or death. Importantly, an untimely recurrence may compromise a unit's mission.

Clinicians confronted by Warfighters with suspected ER can face challenging clinical decisions to include initial identification, medical management, and assessment for return to duty. These decisions include:

- Whether the Warfighter has ER
- When to treat as an outpatient versus inpatient
- When to safely discharge from inpatient treatment
- Who can be safely returned to duty
- How should the Warfighter be restricted/limited ("profiled" or "light duty")
- How long should the duty limitation period be
- Which Warfighters warrant further medical evaluation for an underlying disorder (e.g., a metabolic myopathy)
- Which ER events warrant referral for a medical/physical evaluation board (MEB), which would help determine whether the event might permanently interfere with their ability to continue in military service

This consensus CPG was constructed jointly within the U.S. military to assist clinicians in assessing and managing Warfighters with ER. An algorithm with annotations to assist in the initial management and subsequent risk-stratification process in the event of recurrence and appropriate duty limitations is included in Section 4 of this CPG, along with two companion algorithms for inpatient management of ER (Section 5) and advanced evaluation of high-risk patients (Section 6). A glossary of ER-related terms used in this CPG is also included as Section 7. Specific Warfighter-management questions can be directed to the Warrior Heat- and Exertion-Related Events Collaborative (WHEC) through an Ask the Expert portal at https://www.hprc-online.org/ask-the-expert.

SECTION 4: HOW TO DIAGNOSE AND STRATIFY A WARFIGHTER WITH SUSPECTED ER – ALGORITHM I



Algorithm I. How to Diagnose and Stratify a Warfighter with Suspected Exertional Rhabdomyolysis (ER)

Annotations to Algorithm I

1. Severe Muscle Pain or Cola-Colored Urine

Muscle pain after exercise, particularly a new exercise program, is a common physiologic process that facilitates adaptation. Clinicians frequently encounter Warfighters with exercise-related muscle pain and a need to differentiate potentially pathologic ER from physiologic delayed-onset muscle soreness (DOMS). DOMS is thought to be a process localized principally to extracellular structures, including the muscle fascia and the nervous system, whereas ER is an intracellular pathological condition of the muscle cells. DOMS usually presents within the first 24 hours and peaks at 72 hours after strenuous, prolonged, or unfamiliar exercise training, after a significant amount of eccentric exercise (e.g., pushups, pull-ups, squats, or participation in unaccustomed conditioning exercises). DOMS and ER can have overlapping symptoms, but key symptoms and findings of ER that help distinguish it from typical DOMS include:

- Pain and tenderness to palpation usually are severe or out of proportion to what one would normally expect from the activity,
- Muscle swelling,
- Significant limitation in active and passive range of motion,
- Weakness, especially when the hip and shoulder girdle muscles are involved,
- Presence of cola-colored urine, and/or
- Persistent, non-improving or worsening pain and soreness for more than 5–7 days after the causal activity.

On rare occasions a Warfighter might present with cola-colored urine in the absence of severe muscle pain. This may represent a metabolic myopathy, especially if recurrent or occurring after a low exercise load, but the full differential diagnosis for dark urine must be considered. These Warfighters should undergo the same initial diagnostic evaluation as individuals presenting with classic ER. This includes referral to a medical treatment facility equipped to perform initial laboratory assessments, including serum CK, comprehensive blood chemistry panel, complete blood count (CBC), and a urinalysis (UA) with microscopic examination.

The clinician's judgment is critical to determine the severity of muscle pain and myonecrosis: In many cases, an elevated creatine kinase (CK) level will trigger further evaluation and a clinical determination of the most effective and safest way to manage the Warfighter. The ULN is defined by each laboratory, but is usually about 200 IU/L. However, studies in both Warfighters and athletes have demonstrated that high CK levels (up to 175× ULN) can be tolerated without any symptoms or evidence of AKI in some individuals, leading some experts to suggest a minimum CK laboratory threshold for ER in physically active individuals to 50× ULN for improved specificity.[7] Annotation 4 below details more information on CK, and this CPG's consensus recommendation is for a threshold selection of >5,000 IU/L when making a diagnosis of ER. Importantly, it cannot be overemphasized that an appropriate **exertional history with symptoms**, co-morbidities (e.g., AKI), and clinical judgment should drive management.

2. Primary Exertional Heat Illness

BLUF: The rhabdomyolysis from exertional heat illness (EHI) is a distinct entity from the rhabdomyolysis of exertion.

EHI includes heat exhaustion, heat injury, and heat stroke. All three are significant threats to military populations because of frequent occupational and strenuous physical activities in hot and humid environments. AR 40-501, Chapter 3-27, defines exertional heat illness categories as follows:[8]

- **Heat exhaustion (HE)**: a syndrome of hyperthermia (core temperature at time of event usually ≤40°C or 104°F) with physical collapse or debilitation occurring during or immediately following exertion in the heat, with no more than minor central nervous system dysfunction (such as headache, dizziness). HE resolves rapidly with minimal intervention.
- **Heat injury (HI)**: heat exhaustion with clinical evidence of organ (e.g., liver, renal, stomach) and/or muscle (for example, rhabdomyolysis) damage without sufficient neurological symptoms to be diagnosed as HS.

» **Heat stroke (HS)**: a syndrome of hyperthermia (core temperature at time of event usually >40°C or 104°F), physical collapse or debilitation, and encephalopathy as evidenced by delirium, stupor, or coma, occurring during or immediately following exertion or significant heat exposure. HS can be complicated by organ and/or tissue damage, systemic inflammatory activation, and disseminated intravascular coagulation.

If the primary event is EHI, then the clinician should **exit this rhabdomyolysis algorithm,** and the patient should initially be managed appropriately as heat illness per details in AR 40-501 and military technical bulletin (TB MED) 507, Heat Stress Control and Heat Casualty Management, or other appropriate Service-specific guidance.[3, 8] Return-to-duty decisions will likely be dictated by the nature of the heat disorder. In addition, the 2024 CHAMP CPG on Exertional Heat Illness is an excellent resource for the diagnosis and management of EHI in the military.[2]

3. History, Physical Examination, and Diagnostic Testing

The clinician should perform a focused history and physical examination, as well as limited initial diagnostic testing, to determine if the muscle pain is related to ER or another etiology, as identified in Table 1. Physical exertion within the previous week of presentation and a Warfighter's typical exercise routine should be elicited. The clinician should obtain an exertional history that puts a Warfighter at risk for ER; high-volume, high-intensity, unaccustomed exercise with insufficient time for recovery are known risk factors for ER (described as the concept of "too much, too fast, and too soon"). High-volume eccentric exercises are also more likely to produce significant DOMS and put a Warfighter at risk for ER.[9] In addition, if there is a high intrinsic motivation, competition, or timed test that is meaningful to a Warfighter's career (e.g., for passing schools, promotion boards, etc.) they may place themselves at risk for pushing beyond their physiologic limits.[10] Finally, trainers or leaders who utilize exercise for discipline or push a Warfighter beyond their capability with high-volume or stacked exercise days may also precipitate risk for ER.[11] This adds "timed test" and "tyrannical trainers" to the "too much, too fast, and too soon" risk factors for ER.

Clinicians should also consider other causes or triggers of rhabdomyolysis, such as medications or supplements. The clinician should specifically inquire about and document the use of medications (e.g., statins, antidepressants, antipsychotics, stimulants), dietary supplements (e.g., performance-enhancing, weight-loss, muscle-building, and/or stimulant/caffeine-containing products), and energy drinks. In addition, the clinician should ask about current sleep patterns, nutritional habits, recent vaccinations, and presence of co-existent or recent febrile illnesses, or sickle cell trait (SCT), as these are known or suspected contributors to ER, as well as other etiologies of rhabdomyolysis.[3, 12]

The physical examination is a critical clinical tool in the evaluation of the Warfighter with rhabdomyolysis. Clinicians need to carefully assess involved muscle groups with particular attention to the presence of swelling, as well as range-of-motion and strength assessments. Medical clinicians must be particularly alert for the possibility of an acute compartment syndrome with a low threshold for surgical consultation to consider fasciotomy. Signs and symptoms of an acute compartment syndrome include: pain out of proportion to the injury, paresthesias and sensory deficits, tense and swollen compartments on palpation, decrease or loss of active motion, and severe pain with passive stretch.

If the history and examination indicate an alternate diagnosis, further evaluation should be performed as indicated. Otherwise, the possibility of severe muscle injury should be evaluated with a serum CK, blood chemistry profile (including sodium, potassium, chloride, bicarbonate, BUN, Cr, calcium, magnesium, and phosphorus), CBC, and a urinalysis (UA) with microscopic examination. Current evidence suggests that while pathognomonic for muscle injury, serum myoglobin has low sensitivity and should not be utilized for the initial diagnosis of ER. Serum myoglobin typically peaks around 3 hours after exercise and returns to baseline within 6–24 hours. Serum myoglobin has proven very useful in the prediction of those who will develop AKI from crush-induced rhabdomyolysis, but there are no data to support its application to patients with ER.[13, 14]

4. CK ≥5,000 IU/L

BLUF: It is the consensus of the editors and contributors of this CPG that a CK level of ≥5,000 IU/L accounts for the challenges of a lack of specificity of a lower CK level, the variability of baseline CK levels because of ethnicity or sex, and baseline activity differences, while recognizing the vulnerability of the military population. As always, however, we recognize the judgment of the bedside clinician.

The CHAMP 2020 CPG on ER in Warfighters[15] identified a CK of ≥5× ULN (1,000 IU/I) as the level necessary, in conjunction with an appropriate clinical picture, to make a diagnosis of ER. The CK level was consistent with the level required in AR 40-501, Chapter 3-26b, Exertional rhabdomyolysis.[8] Recently, however, this level has been challenged by evolving literature in military recruits, as well as a new international consensus guideline on the management of ER,[16] both suggesting higher levels to avoid the overdiagnosis of a physiologic event. This literature is briefly reviewed below and rationale provided for the new recommendation of a CK ≥5,000 IU/L, in conjunction with the appropriate clinical picture.

Athletes and Warfighters consistently have higher baseline CK levels than non-active adults as a result of frequent exercise with normal ongoing muscle breakdown and repair.[18, 19] In addition, sex and ethnic variation may contribute to unique baseline CK levels (Figure 1).[20, 21] Studies have consistently noted that African American males and young athletic men have the highest baseline CK levels, and non-African American women have the lowest.[20-23]

Although the case definition for pathologic ER is somewhat controversial, the 2020 guideline utilized the following to enter the management algorithm:[15]

- SEVERE muscle pain and
- Laboratory evidence of muscle injury (CK level ≥5× ULN)

CK ≥5× ULN was chosen as a low threshold designed for high sensitivity, but it has the second-order effect of a very low specificity for ER. Using this criterion is the greatest safety net in assisting the clinician in the initial work-up of this challenging syndrome. Because a CK ≥5× ULN is not uncommon in exercising Warfighters (African American Warfighters may have a baseline rested CK of >600 IU/L), there was the potential for many false-positive diagnoses.[6] While the previous algorithm[15] required an appropriate clinical picture, including severe muscle pain, it was possible to over-diagnose a physiologic event as pathologic. It is also important to acknowledge that CK>5× ULN is currently identified as the criterion for a diagnosis of ER in AR 40-501.[8]

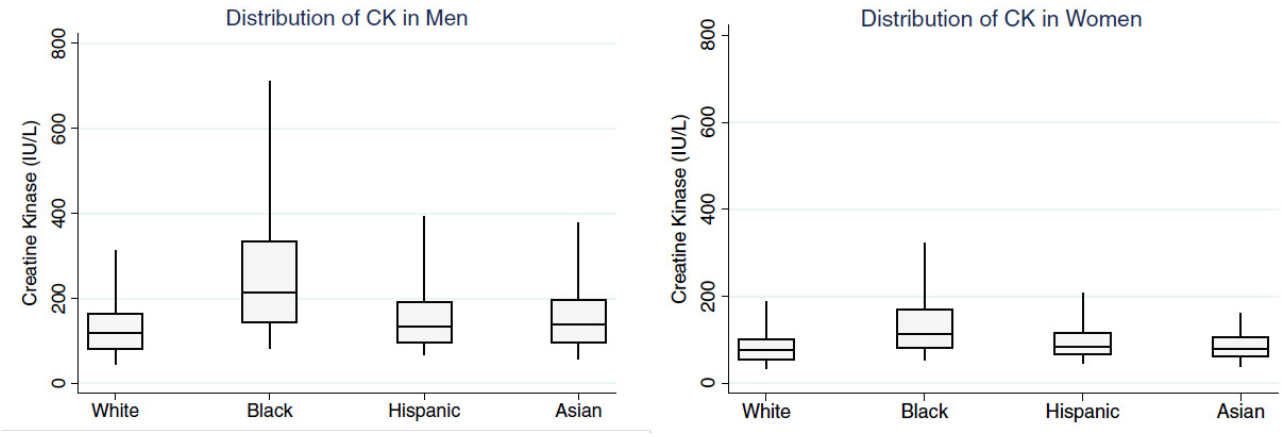


Figure 1. Baseline CK Levels in Nonpregnant Adults >20 After Three Days of No Exercise[17]

In 2024, however, an International Workshop was convened by the European Neuro Muscular Centre (ENMC) in Amsterdam to review the diagnosis and management of exertional rhabdomyolysis.[16] Fundamental to the meeting attendees was the recognition that there is presently no agreed-upon definition for exertional rhabdomyolysis. Attendees concurred that the diagnosis is generally made in combination with the appropriate history, clinical symptoms, and CK elevation. A key citation in the new guidance was from work done at Fort Benning on military recruits.[7] In this study, the researchers studied CK levels during the first several weeks of basic training and concluded that levels >50× the ULN should be considered when making a diagnosis of ER. The key features of rhabdomyolysis from ENMC are identified below.

International consensus conference key features of exertional rhabdomyolysis[16]

1. A CK elevation 12–36 hours 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× the ULN (≥5,000 IU/L) in case of non-exertional rhabdomyolysis
   - >50× the ULN (≥10,000 IU/L) in case of exertional rhabdomyolysis[7, 24]
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) (prolonged immobility, 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).

The criteria presented by international consensus recommend a CK level of ≥10,000 IU/L in conjunction with the clinical presentation of an appropriate exercise trigger and a symptomatic presentation. The editors and contributors of this CPG, however, representing years of experience with Warfighters, recommend moving to a level of ≥5,000 IU/L (with the appropriate clinical picture).

5. Diagnosis of ER

BLUF: Although the case definition for pathologic ER is somewhat controversial, this CPG utilizes the following to enter the management algorithm with a diagnosis of ER:

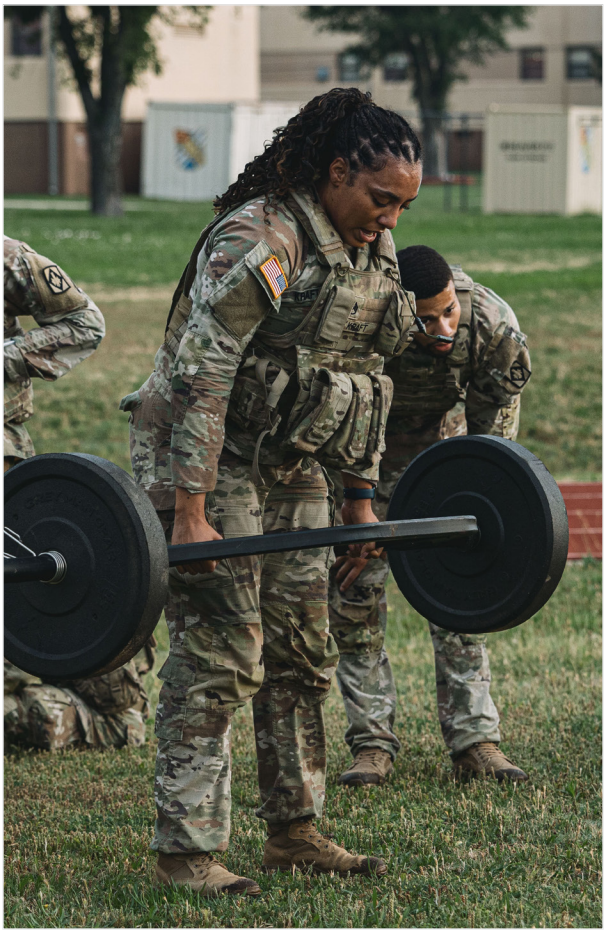
- SEVERE muscle pain (see above for symptoms) and
- Laboratory evidence of muscle injury (CK level ≥5,000 IU/L)

A diagnosis of ER is made when there is severe muscle pain and laboratory evidence of myonecrosis with release of muscle cell contents into the systemic circulation. While CK is the diagnostic gold standard, other cell contents are released, including myoglobin, creatinine, organic acids, potassium, aldolase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). The skeletal muscle subtype CK-MM of the CK enzyme is abundant in skeletal muscle and released as a result of muscle destruction. When clinical evidence of ER is observed, such as severe muscle pain and weakness in the setting of recent strenuous exercise, then CK levels ≥5,000 IU/L are accepted as evidence of significant muscle breakdown and considered consistent with a diagnosis of ER. The clinician is reminded that CK elevations occur for many other reasons, such as inflammatory myopathies and muscular dystrophies (Table 1). Therefore, elevated CK in the absence of exertion would not be considered ER. However, CK remains the accepted gold standard biomarker for diagnosis of rhabdomyolysis, and when there is a recent history of high-risk exertion (too much, too fast, too soon, timed testing, and tyrannical trainer) with an elevated CK, this confirms the diagnosis of ER. Coding is discussed in Appendix 2.

Myoglobin could theoretically be considered as an additional marker for ER because myoglobin does not appear in the blood or urine in the absence of muscle injury. Current evidence, however, suggests that while pathognomonic for muscle injury, serum myoglobin and myoglobinuria are not sensitive for ER. Therefore, they should not be utilized to either make or rule out a definitive di-

agnosis of ER. Myoglobin has been demonstrated to be of value for the prognostication of those who may develop acute kidney injury in cases of traumatic rhabdomyolysis (especially crush injury), but there are no data validating this application for patients with ER.[25]

Although ER is a pathologic condition (and is, by definition, symptomatic), muscle breakdown of a lower degree, as well as soreness after exercise (DOMS), are also normal results of strenuous exercise.[26] Whereas DOMS lasts only a few days and causes little disability, ER can be overwhelming and devastating, with consequences including compartment syndrome, AKI, and death. Although uncommon, ER may reflect an underlying metabolic or myopathic process that predisposes the Warfighter to severe and/or recurrent ER.[27] Accordingly, clinical expertise may be required when treating ER patients, evaluating potential complications from ER, and determining how to stratify the individual's risk for recurrent ER. A multi-disciplinary panel of experts can be very helpful in the diagnostic and prognostic process.[28] Consultation is also available through the CHAMP Warrior Heat- and Exertion-Related Events Collaborative (WHEC) at https://www.hprc-online.org/resources-partners/whec.



6. UA positive for blood but not for RBCs

BLUF: While an onset of dark urine within 24 hours following strenuous exercise is highly suggestive of ER, other etiologies must also be considered such as hematuria (RBCs in the urinary tract), medication side effects, foods, or porphyria. If the etiology of dark-colored urine is unclear, a nephrologist or urologist should be consulted.

After history and physical exam, a urinalysis with microscopy should be performed. Dark or "cola-colored" urine is relatively uncommon, but it may be observed more often following exercise with insufficient hydration. Dark or "cola-colored" urine in the clinical context of acute muscle weakness, pain, or swelling should raise suspicion of exertional rhabdomyolysis, as it can be suggestive of myoglobinuria. This algorithm includes branches for (1) when the urinalysis is positive for blood in the absence of RBCs, which may represent myoglobinuria or hemoglobinuria, (2) positive UA with RBCs, and (3) UA negative for blood. CK levels begin rising about 12 hours after injury and peak at 24–72 hours.[29] Therefore, it is possible, especially in the first 12 hours after strenuous exercise, that an individual will have a CK <5,000 IU/L. Myoglobinuria appears earlier than peak CK, reaching a maximum at about 12 hours post-injury. In cases of expected ER with CK <5,000 IU/L before 12 hours, CK, UA, and metabolic panel should be repeated in approximately 24–72 hours. If CK is ≥5,000 IU/L at that later time, a diagnosis of ER is appropriate.

Urine screening for rhabdomyolysis may be performed by dipstick and urine microscopy (Figure 2). The urine dipstick screens for blood, while microscopy assesses the presence of RBC. If the urine microscopy does not contain RBCs, the positive dipstick reading may reflect the presence of myoglobin in the appropriate clinical setting. Alternatively, a urinalysis that is negative or only has trace amounts of blood has a low probability of containing significant amounts of myoglobin.

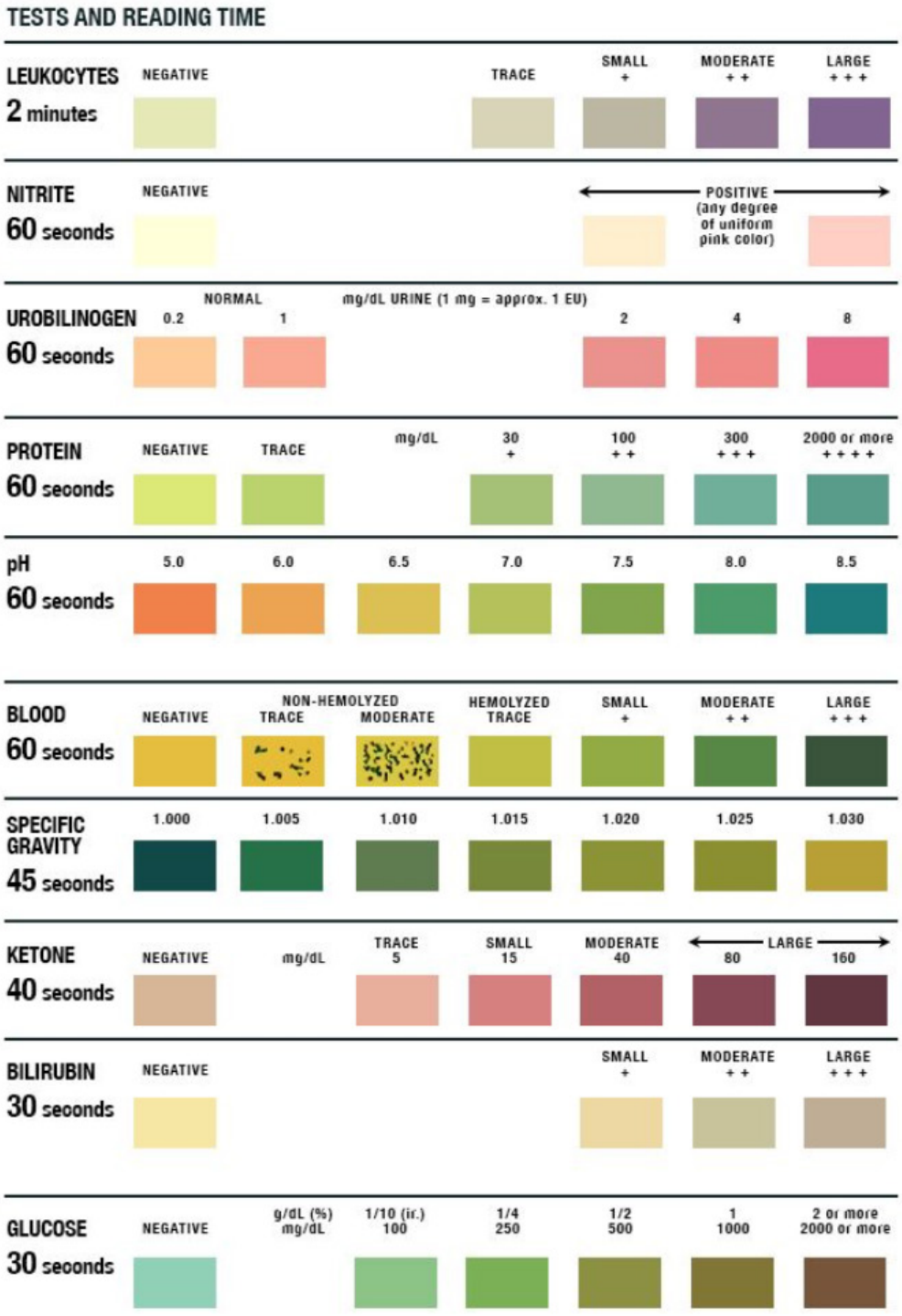


Figure 2. Urinalysis Dipstick[30]

A urinalysis positive for blood, with the absence of RBCs in the sediment, is suggestive of myoglobinuria. However, this result is neither sensitive nor specific for ER, and must be interpreted in the appropriate clinical context and supported by additional labs. Altogether, using any indirect marker of myoglobinuria to diagnose ER or predict ER-associated AKI remains inconclusive.[31-33] Urine myoglobin should be considered if available to confirm the presence of myoglobinuria.

High-intensity or prolonged exercise often results in benign, self-limited hematuria or hemolysis. Exercise-induced hemolysis is quite common and often results in hemoglobinuria, especially after long-distance running or marching (>8–10 miles, longer distances carrying greater risk).[31, 33, 34]. Exercise-induced hemolysis is typically mild, with hemoglobin completely bound to haptoglobin in the blood and metabolized. However, in some cases, the hemolysis is more extensive, leading to hemoglobinuria and occasionally grossly dark urine. The specific cause of erythrocyte rupture is complex, with contributions from membrane fragility due to hyperthermia, lactic acidosis, oxidative damage, and shear stress from forceful ground contacts ("foot strike hemolysis"). Similarly, exercise-induced hematuria is also common, but rarely presents as gross hematuria. Urinalysis with microscopy will reveal the presence of variable quantities of intact RBCs. One study found an incidence of exercise-induced hematuria of 12% among 491 otherwise healthy, 20–50-year-old male subjects after running 5 km with a time limit. When running the same distance without a time limit, the incidence was only 1.3%, suggesting exercise-induced hematuria is strongly related to exercise intensity.[33]

When urine sediment is red or dark, the differential diagnosis also includes hematuria due to glomerular, non-glomerular, and urologic causes (e.g., exercise-induced hematuria, IgA nephropathy, thin basement membrane nephropathy, poststreptococcal glomerulonephritis, pyelonephritis, acute interstitial nephritis, urolithiasis, renal or urologic neoplasm).

Urine discoloration may also be due to medications (Phenazopyridine, rifampin, phenytonin), foods (beets, rhubarb, senna, food dyes), or porphyria (rare). If the cause of dark urine cannot be identified nephrology or urology should be consulted.

7. Consider Renal, Urologic Pathology vs Medications/Foods and Manage as Indicated

An underrecognized military-relevant disorder recently described that should be considered in the differential diagnosis is acute renal (kidney) failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE).[35] ALPE is similar to ER in that it is associated with exercise, but the key difference is that the exercise involves anaerobic stress. Most commonly, ALPE is associated with running sprints, but it also has been reported in a variety of high-intensity short bursts of exercise. Importantly, there should be an absence of dark/cola-colored urine, with serum myoglobin and CK not significantly elevated (less than 9× ULN). In addition to the type of exercise performed, patients with ALPE clinically differ from those with rhabdomyolysis in that they present with significant loin pain, nausea, vomiting, less dehydration, and less oliguria. Loin or flank pain is often described as abdominal pain and can be mistaken for kidney stones, appendicitis, pancreatitis, or gastroenteritis.

While there are no universal diagnostic criteria for ALPE, it should be suspected in the context of AKI without another etiology when there is clinical evidence (see Table 2).[35]

Table 2. ALPE vs Rhabomyolysis-induced Acute Kidney Injury

Clinical Indicator	ALPE	Rhabomyolysis-induced Acute Kidney Injury
Extent of exercise	+ (recent intense, short-term)	+++ (long-standing)
Kinds of exercise	Short track (anaerobic)	Marathon, mountain climbing (aerobic)
Urine volume	Nonoliguric	Oliguric
Dark urine	–	+++
Loin pain	+++ (severe paraspinal back pain several hours after exercise)	–
Nausea, vomiting, slight fever	++	+
Dehydration	+	+++
Serum myoglobin, CK	Normal or slightly increased (mild; <7× the reference value for serum myoglobin, and <9× the reference value for CK)	Remarkably increased
Delayed CT scan after contrast medium	Patchy*	Diffuse

*Wedge-shaped contrast enhancement of the kidney on plain CT from a few to 72 hours after the administration of a contrast medium. However, delayed CT after administration of the contrast medium is not essential to making a diagnosis of ALPE and should be avoided in the presence of an AKI.

In the military population, ALPE should be particularly considered after physical fitness tests such as the Marine and Army fitness tests.[36] Factors that can predispose a Warfighter to ALPE include deconditioning, dehydration, and NSAID use. Hypouricemia may also be a prominent metabolic/genetic factor.[37] The exact pathophysiology of ALPE is unknown, but a proposed mechanism is that it results from reversible renal ischemia with increased oxidative stress and ensuing renal vasoconstriction. This pathophysiology manifests as diffuse, patchy, wedge-shaped contrast enhancement on delayed (6–48 hours) CT imaging. Renal biopsy may demonstrate acute tubular necrosis. ALPE is generally considered a benign condition, and the prognosis is favorable.[38] Treatment is conservative with pain control, and IV hydration if hypovolemic. In contrast to ER, large-volume resuscitation is not needed and IV fluids should be given based on volume status. The need for hemodialysis is infrequent, but the patient should be carefully monitored for acute indications; creatinine typically plateaus within 4 days. A gradual approach to return-to-duty should be implemented. The rate of occurrence, reoccurrence, and long-term consequences of ALPE are currently unknown. If a case of ALPE is diagnosed or suspected, consultation is available through the CHAMP Warfighter Heat- and Exertion-Related Events Collaborative (WHEC) at https://www.hprc-online.org/resources-partners/whec.

8. Consider Duty Profile

The Warfighter with signs/symptoms probable for DOMS (physiologic muscle breakdown: ICD-10: M62.9 – disorder of muscle, unspecified) may be considered for a temporary profile with limited indoor duty for the rest of the day and no regular physical training, with a mandatory medical re-evaluation in 24–72 hours with repeat UA and CK to re-assess for possible ER as clinically indicated. Oral fluid intake should be encouraged (Appendix 1, Phase 1).

9. CK ≥5,000 IU/L

See annotation 4.

10. Follow-up Visit for Duty Profile

At the 24–72 hours follow-up, a Warfighter diagnosed with physiologic muscle breakdown (DOMS) may continue a limited-duty profile, if previously ordered, for up to 72 hours, after which activities can be advanced as tolerated in accordance with the recommendations of Phase 2 of Appendix 1. The clinician should consider referral to physical therapy or an athletic trainer for rehabilitation or reconditioning as clinically indicated. Although consideration can be given to a short course of acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief, muscle pain serves as an important guide in return to activity and should not be masked. In addition, excessive doses of NSAIDs and/or acetaminophen can result in nephrotoxicity or hepatotoxicity, respectively.[39] This risk may be heightened following the stress of significant exertional muscle breakdown. If on re-evaluation, however, symptoms are not improving, and CK is <5,000 IU/L, the clinician should manage as clinically indicated.

11. Initial High-risk Markers

BLUF: The presence of any high-risk markers warrants triage/referral of the patient to a clinician and/or medical facility familiar with the diagnosis and management of ER (e.g., neurologist, nephrologist, cardiologist, or sports medicine physician). This will likely include inpatient admission.

After diagnosing a Warfighter with ER, the clinician must carefully screen for initial "high-risk" markers that have been shown to place the patient at increased risk for complications. High-risk markers (presented in Algorithm 1 Box 11) are also given here in Table 3.

Table 3. Initial High-risk Markers

- CK ≥20,000 IU/L
- Potential compartment syndrome
- Acute kidney injury (serum creatinine increase of ≥0.3 mg/dL within 48 hours,
  - OR serum creatinine 1.5 times baseline level within previous 7 days,
  - OR a urine output of <0.5 mL/kg/hr for 6 to 12 hours)
- McMahon score ≥6
- Dark urine and/or confirmed myoglobinuria
- Metabolic and/or electrolyte abnormality (e.g., hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, acidosis)
- Sickle cell trait carrier
- Elevated troponin*
- Limited patient follow-up (e.g., Warfighter lives alone)

*Troponin is not routinely utilized in the management of ER, and should be ordered only as clinically indicated. (See Algorithm II, Annotation 2, for further discussion).

The recently developed McMahon score (https://www.mdcalc.com/calc/4017/mcmahon-score-rhabdomyolysis) is a retrospectively validated tool that predicts those at greatest risk for AKI needing renal replacement therapy (RRT) or for death.[40, 41] The McMahon algorithm demonstrates that the risk of acute kidney injury requiring RRT increases with a CK >40,000 IU/L. Other risk factors are age >50 years, female sex, initial creatinine >1.4 mg/dL, and additional metabolic changes (hypocalcemia, hyperphosphatemia, acidosis; Table 4). A McMahon risk score, calculated on admission, of 6 or greater is predictive of severe AKI potentially requiring renal replacement therapy (RRT) or risk of death.

- <6 = Low risk: Recommend usual care – 3% risk of death or AKI requiring RRT.
- ≥6 = Not low risk: Initiate renal protective therapy, including high-volume fluid resuscitation to urine output 1–2 mL/kg/hr – 52% risk of death or AKI requiring RRT at scores ≥10.

Table 4. McMahon Score[40]

Variable	Risk Level	Score
Age (years)	>50 to ≤70	1.5
	>70 to ≤80	2.5
	>80	3
Sex	Female	1
Initial creatinine	1.4 to 2.2 mg/dL	1.5
	>2.2 mg/dL	3
Initial Calcium	<7.5 mg/dL	2
Initial CK	>40,000 IU/L	2
Origin	Not from seizures, syncope, exercise, statis, or myositis	3
Initial Phosphate	4.0 to 5.4 mg/L	1.5
	>5.4 mg/L	3
Initial bicarbonate	<19 mEq/L	2

Although a peak CK of ≥5,000 IU/L is reported to be 55% specific and 83% sensitive for predicting AKI for those with traumatic rhabdomyolysis, ER patients with mild symptoms and serum CK levels ≤20,000 IU/L are considered at low risk for AKI and may be treated as outpatients (so long as there are no other features suggesting higher risk for other complications).[42] Outpatient treatment in such patients consists of oral fluid intake, limited physical activity, and careful follow-up. This CPG identifies a CK ≥20,000 IU/L as an initial high-risk marker and recommends triage to a higher level of care for possible inpatient treatment.

ER can be associated with the development of acute compartment syndrome (ACS).[43] ACS occurs when the tissue pressure within a closed muscle compartment exceeds the perfusion pressure and results in muscle and nerve ischemia. Early signs of ACS include severe pain, worse pain with passive stretching, decreased peripheral sensation, and swelling. Paresis and the loss of a pulse are late signs. Clinical suspicion should be high, as surgical intervention for a fasciotomy may be required to prevent ischemic necrosis. An orthopedic or general surgeon should be consulted emergently if compartment syndrome is suspected.

Common metabolic abnormalities considered "high risk" include, but are not limited to, hyper- and hypokalemia, acidosis, hyperphosphatemia, and hyponatremia.[44] If only mild in degree, these abnormalities do not, in and of themselves, warrant admission, but do necessitate close follow-up, with immediate access to labora-

tory capabilities and proximity to an inpatient treatment facility. However, moderate to severe electrolyte and acid/base derangements do necessitate inpatient treatment. These "high-risk" markers are a guide, and do not supersede clinical judgment.

Finally, the clinician should be familiar with exertional collapse associated with sickle cell trait (ECAST).[45] ECAST is seen in sickle cell trait positive (SCT+) individuals demonstrating myopathic clinical presentations associated with exercise without initial evidence of central nervous system (CNS) dysfunction. Manifestations range from ischemic muscle cramps to fulminant collapse, typically triggered by intense physical effort in conjunction with limited recovery. Symptoms include out-of-proportion muscle weakness and pain, particularly in the legs and lower back, along with potential modest temperature elevation. Unlike many other exertional injuries, there are generally no initial alterations in conscious state or evidence of CNS dysfunction. However, if not recognized quickly and treatment is not initiated promptly, ECAST may progress to obtundation, unconsciousness, and even exertional sudden death.[46] Although diagnostic criteria are still developing, ECAST diagnosis requires the following:

- SCT+ individual
- A high-intensity exertional event or activity
- Unusual and progressive muscle weakness and pain, most commonly in the lower extremity and back
- Absence of initial CNS dysfunction

Determination of SCT status is critical knowledge for the entire primary and covering medical staff, as it is a cornerstone in the differential diagnosis of an exertional collapse. Key signs and symptoms of ECAST may include muscle weakness, muscle pain, feeling of inability to continue with exercise, falling to the ground, increased respiratory rate, and feeling like one is unable to catch their breath. ECAST requires immediate recognition and emergency management to include aggressive fluid resuscitation, oxygen therapy if hypoxemic (e.g., SpO_2 <94%), and close monitoring and treatment of metabolic and electrolyte derangements. Due to the high mortality associated with ECAST, consider transfer to a tertiary care facility prepared to accommodate critically ill patients.

12. Individualize Outpatient vs Inpatient Management

BLUF: The decision to hospitalize the Warfighter should be contingent upon factors such as metabolic abnormalities, AKI, Warfighter status (i.e., trainee, recruit, barracks dweller, and limited patient follow-up), and CK levels. The final decision for inpatient versus outpatient management rests on clinical judgment.

The Warfighter diagnosed with ER, but without high-risk markers, should be considered for outpatient management. There is significant controversy about using CK level as an admission criterion. Case reports reveal a wide CK range that has been successfully managed in an outpatient setting, with some expert opinions suggesting that increasing oral fluid intake may be reasonable for athletes with CK levels of 20,000–50,000 IU/L and no additional high-risk features.[15, 47, 48] This guideline, however, recommends that, in a military population, a CK level of <20,000 IU/L without any high-risk features in a reliable patient with follow-up should be considered for outpatient management. Warfighters with CK ≥20,000 IU/L should be considered for inpatient management.

Warfighters stratified to outpatient management should be encouraged to monitor urine output with a goal of approximately 200 mL/hr, or 1 liter every 6 hours. The Warfighter should be placed on quarters, with follow-up evaluation within 24–72 hours. Follow-up evaluation should assess symptoms and any evidence of complications, and should include a complete set of vitals, a UA, repeat CK, and basic metabolic panel. If CK continues to downtrend, renal function improves or normalizes, symptoms improve, and no complications emerge, then the Warfighter should be re-evaluated as an outpatient until symptoms resolve and profiled accordingly. Any worsening symptoms, metabolic abnormalities, worsening renal function, or increasing CK levels should prompt admission for management with intravenous (IV) fluids. While this CPG identifies 20,000 IU/L as a point of discernment for inpatient versus outpatient management, clinical judgement that integrates the context of lab timing and the individual patient presentation should guide the final triage decision.

13. Profile and Follow-up

The Warfighter should be placed on a limited duty profile that excludes field duty (e.g., extended marching, obstacle courses, and land navigation) for the duration of the initial, phase 1, recovery period. The profile must also limit aerobic and anaerobic exercise per Appendix 1 recommendations. The Warfighter should be re-evaluated in 24–72 hours. If CK is still elevated and/or the UA is still positive at this time, the limited duty profile should be continued with the patient being reevaluated at 24- to 72-hour intervals.

A graduated return-to-duty protocol, per Appendix 1, may be initiated when the Warfighter is clinically improved, with return of normal joint range of motion, no evidence of myalgia, a CK level <5,000 IU/L and/or downtrending, and a normal UA. It is strongly recommended that a physical/occupational therapist or athletic trainer supervise the return-to-duty and reconditioning program. Potential contributing risk factors should be discussed with the patient, as well as mitigation strategies, as applicable. The authors of this CPG recommend repeat CK testing only when there is no demonstration of clinical improvement within 1–2 weeks, or there is a clinical relapse.

14. Recurrence Risk Stratification at 2 Weeks from Date of Injury

To define the case as "high risk" for recurrence that may require consultation, this CPG identifies that at least one of the following conditions must exist:[15]

- Delayed clinical recovery (despite more than a week of activity restriction).
- Persistent CK elevation >1,000 IU/L, despite rest for at least 2 weeks, but consideration should be given to sex and ethnicity (see Figure 1).
- ER complicated by AKI that does not return to baseline within 2 weeks as evidenced by elevations in BUN/creatinine.
- ER after low to moderate workload.
- Personal or family history of:
  - ER.
  - recurrent muscle cramps or severe muscle pain that interferes with activities of daily living or military performance.
  - malignant hyperthermia or unexplained complications or family history of death following general anesthesia.
  - (if personal status unknown) sickle cell disease or trait.
- Family history of sudden cardiac death.
- ER complicated by drug or dietary supplement use (if the offending agent cannot be discontinued):
  - Drugs increasing risk for ER: statins, NSAIDs, antipsychotics (e.g., haloperidol), antidepressants (e.g., selective serotonin reuptake inhibitors), stimulants (amphetamines, methylphenidate, MDMA, cocaine, LSD).[49]
  - Dietary supplements increasing risk for ER: stimulants (e.g., caffeine, synephrine, octopamine, yohimbine, ephedra).
    - For a list of other stimulants in supplements (see https://www.opss.org/article/stimulants-dietary-supplements).
  - Although supplements do not imply a medical condition that would necessarily warrant MEB or detailed work-up, individual as well as unit education may be warranted.
- Personal history of significant heat injury.
- CK peak >100,000 IU/L.

To define the case as "low risk" for recurrence, the following conditions must be met:

- None of the high-risk conditions should exist.
- A full clinical recovery within 1–2 weeks (symptoms and exam findings normalized).
- **At least one** of the following conditions must also exist:
  - Physically trained Warfighter with a history of recent high-risk training.
  - No personal and family history of ER or previous reporting of exercise-induced severe muscle pain, muscle cramps, or heat injury.
  - Existence of other ER cases in the same training unit.
  - Concomitant substance use that has been discontinued.
  - Identifiable period of sleep and/or nutrition deficit.
  - Concomitant viral illness or other infectious disease.

Genetic causes have been identified as potential etiologies for recurrent ER. Krujit *et al.* (2025) specifically cite the work by Scalco *et al.* (2016) for the useful "RHABDO" mnemonic to identify patients at potential risk (Table 5).[16, 50]

Table 5. Genetic Etiology Using the RHABDO Acronym for Rhabdomyolysis

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 IU/L ULN)
D	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)

15. Complete Appendix 1

See Appendix 1: Return-to-duty Guidelines for Physiologic Muscle Breakdown and Low-risk Warfighters with Exertional Rhabdomyolysis.

16. Abnormal Recurrence Risk Stratification

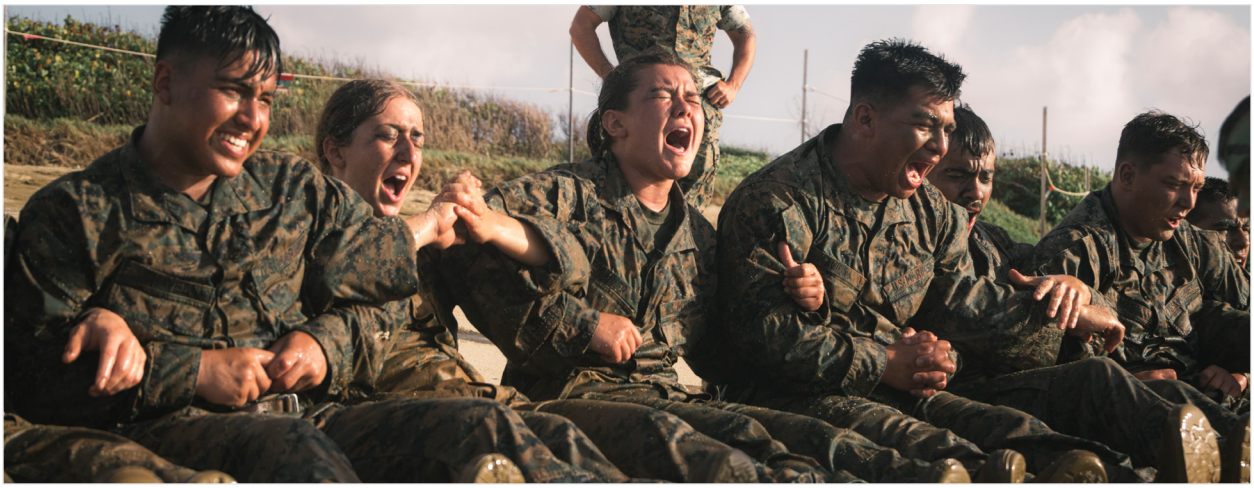
If at 2 weeks after injury, clinical indicators (laboratory values, physical exam findings) are assessed as high risk for potential recurrence, the Warfighter should be referred to or discussed with an appropriate specialist (e.g., neuromuscular specialist, nephrologist, sports medicine physician) or regional consultant for further management and potential evaluation for an underlying disorder that may predispose to recurrent injury. Consultation is also available through the CHAMP Warrior Heat- and Exertion-Related Events Collaborative (WHEC) at https://www.hprc-online.org/resources-partners/whec. The evaluation may include, but is not limited to, one or more of the following:

- genomic testing
- electromyography (EMG)
- muscle biopsy
- caffeine-halothane contracture test
- exercise challenges

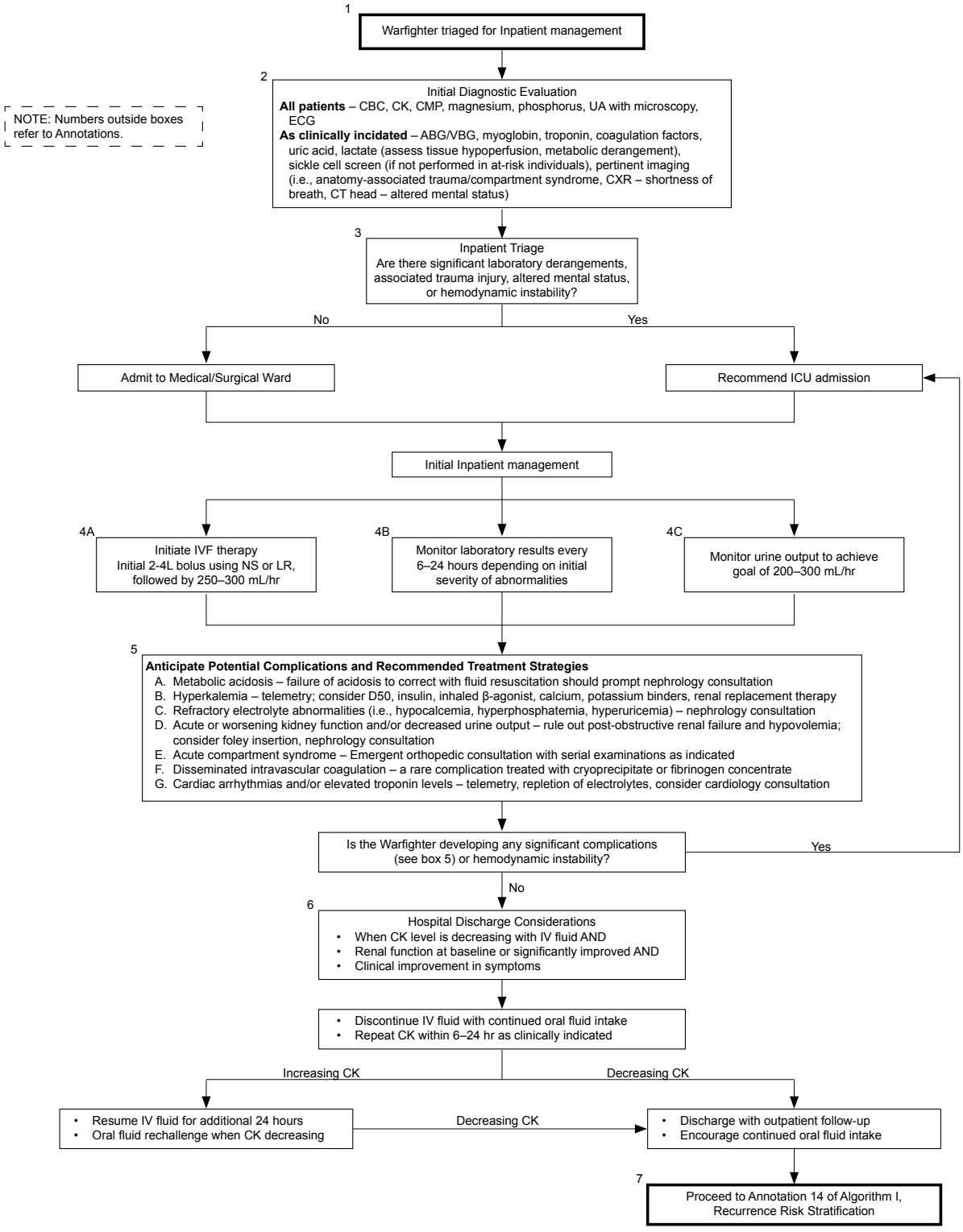
While EMG abnormalities secondary to a rhabdomyolysis event are generally resolved at about 8 weeks after the event, it can take longer for EMG changes to normalize. To avoid false positives, waiting until 12 weeks post-event may be recommended. Return to duty and profiling are individualized based on results of testing and are presented in Algorithm III.

17. Inpatient Management

Patients with CK levels ≥20,000 IU/L or any significant high-risk markers may require further testing and observation in an inpatient setting. Accordingly, a higher level of care should be considered, and the patient should be managed per Algorithm II.



SECTION 5: INPATIENT MANAGEMENT FOR THE WARFIGHTER WITH ER – ALGORITHM II



Algorithm II. Inpatient Management for the Warfighter with Exertional Rhabdomyolysis

Annotations to Algorithm II

1. Patient Referred for Inpatient Care Due to Initial High-risk Markers

Review the high-risk markers that prompted the Warfighter's referral to a higher level of care, as outlined in Algorithm 1, Annotation 11, or those that present to the Emergency Department with concerning symptoms of ER. These high-risk markers (see also Table 3) serve as a clinical guide to assist clinicians in determining whether hospitalization or outpatient management is more appropriate for the individual. The editors and contributors believe patients with any high-risk markers should be strongly considered for admission, even if the initial CK level is <20,000 IU/L.

2. Initial Diagnostic Evaluation

The facility should have the capability for additional laboratory evaluations, short-term observation, and access to large quantities of intravenous (IV) fluids. Initial workup that should be obtained on all patients includes CBC (assess for leukocytosis, hemoconcentration), comprehensive metabolic profile (CMP: include liver function tests and calcium), magnesium, phosphorus-CK, and UA with microscopy and ECG.

Additional lab tests may be obtained as clinically indicated, including ABG/VBG (assess severity of metabolic acidosis), lactate (assess tissue hypoperfusion, metabolic derangement), coagulation factors (PT, aPTT, fibrinogen, fibrin degradation products if at risk for disseminated intravascular coagulation), uric acid, myoglobin, sickle cell screen (if not previously performed in at-risk individuals), and troponin.[49]

Imaging recommendations include CT of head if the individual has a history of head trauma, unwitnessed collapse, or altered mental status. Chest X-ray is useful if there are symptoms of chest pain or shortness of breath. Additional imaging may be required if there is concern for compartment syndrome.

An electrocardiogram (ECG) should be obtained to assist in the assessment and management of hyperkalemia, arrhythmia, and/or chest pain. Clinical indicators for troponin testing include cardiovascular symptoms or signs of hemodynamic compromise, but there is substantial crossover with the presentation of ER. Chest pain is the hallmark symptom of myocardial involvement, but other symptoms such as dyspnea and fatigue may also occur with ER. Hypotension occurs due to decreased cardiac output in myocardial injury, but also from hypovolemia and the systemic effects associated with ER. Although troponin testing is highly specific for myocardial infarction, there are non-ischemic conditions that cause myocardial necrosis and troponin elevation, such as pulmonary embolus, myocarditis, inflammatory heart disease, and Takotsubo Syndrome (TTS or stress-induced cardiomyopathy). Furthermore, troponin may be elevated in non-cardiac conditions such as chronic renal failure, sepsis, and physical exertion. Therefore, the clinician must consider the clinical context and make a judicious determination before ordering troponin testing.

Elevated troponin in ER is associated with increased mortality[51, 52] and should prompt further evaluation in accordance with acute coronary syndrome (ACS) guidelines, starting with an immediate electrocardiogram to assess for ischemia (ST segment elevation or depression, new Q waves) and consideration of cardiology consultation to assess for ACS, TTS, or other cardiac etiologies. Troponin is frequently elevated after endurance athletic events, with cardiac troponin T (cTnT) rising in 27% of cyclists,[53] while marathon runners showed a post-event increase of 52% in cTnT,[53] 61% in cardiac Troponin I (cTnI), and 81% in highly sensitive cTnT.[54] Unlike the injury patterns seen in acute myocardial infarction (AMI), cardiac MRI studies after exercise-induced troponin elevation do not show signs of myocardial inflammation or fibrosis.[55] Troponin kinetics also differ between AMI and exertion, with normalization of troponin levels taking up to 14 days for AMI but only 25–72 hours after exercise-induced rises.[56, 57] A meta-analysis of studies assessing exercise-induced hs-cTnT elevations showed that post-exercise levels increased up to 7.5× baseline, and the upper reference limit (URL) rose from 19 to 390 ng/L.[56] These values and kinetics can help guide a treatment plan that may include delayed ischemic evaluation in the absence of an urgent indication for revascularization (e.g., STEMI).

3. Inpatient Triage

Most patients with ER can be safely managed on a medical ward, but those patients with significant laboratory abnormalities, associated trauma injuries, altered mental status, or hemodynamic instability should be managed in the intensive care unit (ICU). ICU admission is warranted for individuals requiring invasive cardiopulmonary monitoring, developing respiratory distress (i.e., hypoxia, pulmonary edema), worsening renal function/poor urine output (in anticipation for RRT), severe electrolyte or metabolic disturbances, disseminated intravascular coagulation, or life-threatening cardiac arrhythmias. In addition, patients who develop acute compartment syndrome typically require surgical fasciotomy and close monitoring either in the ICU or surgical ward.

4. Initial Inpatient Management

The acute treatment of the Warfighter with ER is focused on preventing complications and is guided by continual assessment of vital signs, serial physical examinations, serial laboratory studies, and urine output.

A. IV Fluid Therapy

ER patients who are admitted require aggressive IV fluid therapy with isotonic fluids (lactated Ringer's [LR] solution preferred, or normal saline [NS]), which should be initiated and then maintained to target urine output of 200–300 mL/hr.[50, 58, 59] Strict "in and out" measurements are critical in the management of ER and can be done without the need for Foley catheterization to minimize risk for catheter-associated urinary tract infection. In general, ER in healthy Warfighters responds well to IV fluids alone without need for alkalization. Most patients with ER present with hypovolemia, which requires fluid bolus resuscitation. Initial fluid bolus typically ranges 2–6 L (1–2 L/hr), followed by 250–300 mL/hr to maintain urine output of 200–300 mL/hr, which should be maintained until renal function improves and CK levels begin to decline unless volume overload develops.

B. Monitoring Laboratory Results

The frequency of laboratory monitoring is based on degree of ER, metabolic abnormalities, and renal function. The average time to peak at onset of muscle injury is 24–48 hours for creatinine, 24–72 hours for CK, 3–4 days for AST, and 4–5 days for ALT. In mild cases of ER, it is reasonable to check CMP, magnesium, phosphorus, and CK levels every 24 hours. More critically ill ER patients—specifically when initial electrolyte abnormalities, acid-base disorders, or renal injury are present—may require closer surveillance (i.e., every 6, 8, or 12 hours). Transaminases and CK levels typically are last to fall and often remain abnormal at discharge.

Elevated transaminase levels in the setting of ER are expected, and generally result from myocyte release and cause confusion with hepatocellular damage. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are present in both hepatic and skeletal muscle; however, ALT is more specific to the liver. In ER, AST tends to peak at 3 to 4 days and ALT peaks at 4 to 5 days post-injury. In severe ER, transaminases may remain elevated for 2 to 3 weeks. Investigation for coexisting hepatocellular damage is not indicated in patients who have downtrending transaminases once they have peaked at their expected interval. However, those who have an abnormal transaminase trajectory, elevated bilirubin, or γ-glutamyl transferase may require additional investigation for liver disease.[60, 61]

C. Monitor Urine Output

IV fluid rates should be titrated to the recommended urine output goal of 200–300 mL/hr while avoiding volume overload. If there has been no urine output after initial fluid resuscitation, the clinician needs to reassess if the patient has been appropriately volume resuscitated. These tests can include evaluating mean arterial pressures, performing a passive leg raise, or using point of care ultrasound (POCUS) if available. If the patient has been appropriately volume resuscitated, but there is no urine output, ensure there is no evidence of post-obstructive renal failure (i.e., bladder scan, renal ultrasound).

In the absence of symptomatic volume overload, furosemide (or other diuretics) should not be used solely for the purpose of increasing urine output, due to its effects on urine acidification and possible precipitation of urine myoglobin. Overload and flash pulmonary edema may occur with the aggressive fluid volumes administered, and the Warfighter must be evaluated periodical-

ly for signs of fluid overload, including dyspnea, rales, and evidence of abdominal compartment syndrome (painful, tense, or swollen abdomen). Furosemide may alleviate pulmonary edema and should be considered in that setting. Volume overload may prompt transfer to the ICU, and minimally invasive and invasive techniques, if utilized for volume assessment and management, should be performed under the direction of a critical care intensivist and appropriately trained hospitalist.

5. Complications Associated with ER

A. Metabolic Acidosis

BLUF: The editors and contributors of this 2025 CPG update currently do not recommend the routine utilization of either mannitol or urinary alkalinization for the management of the Warfighter with ER. There is conflicting literature on the value added of these strategies, and concerns for second-order effects, including hypocalcemia and volume overload; instead, nephrology consultation should be strongly considered.[62-64]

I. Although no large, randomized trials suggest any clinical advantage to urine alkalinization over aggressive hydration for patients with ER, a retrospective review of 56 traumatic rhabdomyolysis patients with CK >10,000 IU/L suggests that a protocol of forced alkaline diuresis with mannitol and bicarbonate significantly decreases the odds for developing AKI (OR = 0.175).[65, 66]

II. If being pursued, urine alkalinization can be considered in patients who are volume resuscitated, meeting UOP goals, and having ongoing muscle breakdown. To accomplish this, dilute 2 ampoules (2 amps; 100mL) of sodium bicarbonate in D5W 1L administered at a rate of 75–125 mL/hr.

III. Sodium bicarbonate should NOT be used for patients who have:
   1. Hypocalcemia
   2. Alkalemia (for bicarbonate use, serum pH must be <7.5 and serum bicarb must be <30)
   3. Volume overload

IV. Labs need to be obtained frequently—every 2 hours, with Chem10 (with specific attention to K+ [potassium] and Ca++ [calcium]), ABG (pH), and UA (pH).

V. Goal is urine pH >6.5, which should be reached in 4 hours; if not, then alkalinization should be stopped and nephrology consulted.

B. Hyperkalemia

Potassium released from damaged muscles and decreased urinary clearance from acute kidney injury can be potentially life-threatening. The most important effect of hyperkalemia is a change in cardiac excitability; the initial presence of tall, peaked T waves can occur with a potassium >6.5 mEq/dL. Continuous ECG monitoring should be considered in the event of ECG changes or if the potassium level is >5.5 mEq/dL.

Utilize calcium gluconate or calcium chloride to stabilize the cardiac myocytes if EKG changes are consistent with hyperkalemia, and initiate treatment to shift potassium intracellularly. Inhaled beta-agonists and intravenous insulin with dextrose (D50) typically lower serum potassium by 0.7 to 1.2 mmol/L within 1 to 2 hours.[67] If there is inadequate cardiac stabilization after initial therapy, nephrology consultation is warranted, and emergent dialysis should be initiated. Additional options to facilitate potassium removal, such as loop or thiazide diuretics may be used in collaboration with nephrology. Potassium-binding agents (e.g., sodium polystyrene sulfonate, patiromer, or sodium zirconium cyclosilicate) can also reduce serum potassium, but their delayed onset (24–48 hours) limits their utility in acute management. Serum potassium should be measured one hour and 2 hours after the initial intervention. If hyperkalemia is present without cardiac manifestations/EKG changes, continue to treat underlying cause with IV fluid resuscitation and other adjuncts, as needed.

C. Additional Electrolyte Abnormalities

a. Hypocalcemia. Deposition of calcium in muscle, which occurs early in ER, is directly related to the degree of muscle destruction and administration of calcium. Reversal of hypocalcemia may, in fact, worsen heterotopic calcification and exacerbate hypercalcemia during the resolution phase. Hypocalce-

mia should be treated only if the patient has evidence of cardiac arrhythmias or seizures.

b. **Hyperphosphatemia.** Phosphate is generally very well regulated in the body. The development and persistence of hyperphosphatemia can be due to either excess release, diminished excretion, or both. Significant changes in phosphate levels are cause for concern, especially if persistent and/or >5.4 mg/dL, as this is both a marker of serious rhabdomyolysis and a possible indication for dialysis. Persistent hyperphosphatemia requires an evaluation to determine the presence of ongoing muscle damage, and the extent and progression of a decline in renal function. Nephrology should always be included in cases involving hyperphosphatemia.

c. **Hyperuricemia.** Breakdown of skeletal muscles leads to the release and subsequent degradation of purine nucleotides from injured myocytes leading to increased production of uric acid. These substrates can increase the risk of renal injury. Primary treatment of elevated uric acid levels is aggressive hydration. Urate-lowering therapy is generally not indicated except in severe hyperuricemia or uric acid nephropathy.

D. Acute Kidney Injury

The term "acute renal failure" includes "acute kidney injury" (AKI), which is defined as any of the following:[68]

- Increase in serum creatinine by 0.3 mg/dL (× 26.5 mol/L) within 48 hours; or
- Increase in serum creatinine to 1.5× baseline, which is known or presumed to have occurred within the previous 7 days; or
- Urine output (UOP) <0.5 mL/kg/hr for 6 hours.

This widely-accepted definition was proposed by the Acute Kidney Injury Network (AKIN) and supported by the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines.[69] These criteria include both absolute and percentage changes in serum creatinine to accommodate variations related to age, sex, and body mass index, and to reduce the need for a baseline creatinine; the criteria do require at least two creatinine values within 48 hours. Although urinary output (UOP) was included in the criteria based on its predictive importance, UOP may not be routinely measured in non-ICU settings. A diagnosis of AKI based on UOP criteria alone requires exclusion of urinary tract obstruction or other reversible causes of reduced UOP. These criteria should be used in the context of clinical presentation and after adequate fluid resuscitation when applicable. AKI is further staged in Table 6.

Table 6. Acute Kidney Injury Staged for Severity According to AKIN/KDIGO Criteria

Stage	Serum Creatinine	Urine Output
1	1.5–1.9× baseline OR ≥0.3 mg/dL (≥26.5 μmol/L increase)	<0.5 mL/kg/hr for 6–12 hours
2	2.0–2.9× baseline	<0.5 mL/kg/hr for ≥12 hours
3	3.0× baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 μmol/L increase) OR In patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/hr for ≥24 hours OR Anuria for ≥12 hours

Several studies have demonstrated increased risk of AKI in patients with ER and CK levels in the range of 5,000–40,000 IU/L. The incidence of AKI in patients hospitalized for ER in a 2024 retrospective cohort study was 8.5%.[70] The risk of AKI was significantly higher in patients who used NSAIDs before admission. This is an important clinical finding, as many Warfighters are routinely prescribed NSAIDs. Recovery of AKI in ER is excellent with adequate fluid resuscitation, often within 24–48 hours.

Nephrology consultation is advised in patients with worsening renal function, oliguria or anuria, or life-threatening electrolyte abnormalities. The indication for renal replacement therapy (RRT) is based on the judgment of the consultant nephrologist. Criteria to consider RRT are not based upon serum creatine kinase or myoglobin levels, but on the status of renal impairment, with complications such as life-threatening hyperkalemia, hypercalcemia, uremia, anuria, or volume overload without response to diuretic therapy.[65, 68] RRT is required in only 4–20% of patients with AKI caused by ER.[71]

DoD clinicians can contact nephrology at any time by emailing their Surgeon General specialty advisor for nephrology or, if no urgent recommendations are needed, sending a consult via DHA's Global Teleconsultation Portal (GTP.Health.mil).

E. Compartment Syndrome

Acute compartment syndrome (ACS) is a well-described potential late complication of ER.[15, 44] In the proper clinical setting, the following signs and symptoms should raise suspicion of a diagnosis of compartment syndrome:

- Pain disproportionate to the injury
- Pain with passive stretching of a muscle
- Paresthesia of the involved extremity
- Diminished distal pulses
- Increased tension or turgor of the involved muscle groups

Clinical suspicion should be followed by urgent consultation with a general or orthopedic surgeon to expeditiously measure compartment pressures. While tissue pressures >30 mm Hg should prompt consideration for surgical fasciotomy, all management decisions are to be guided by the treating consultant.

F. Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a rare complication of ER resulting from massive skeletal muscle breakdown triggering a release of procoagulants, systemic coagulation activation, and fibrinolysis. The prevention of DIC is prompt treatment of rhabdomyolysis. DIC often requires blood products (i.e., platelets, fresh frozen plasma, cryoprecipitate, or fibrinogen), and should be managed by a critical care intensivist.

G. Cardiac Arrhythmias and/or Elevated Troponin Levels

Cardiac arrhythmias are common in the presence of severe electrolyte abnormalities—primarily hyperkalemia, hypocalcemia, and hyperphosphatemia. Correction of electrolyte abnormalities minimizes risk of arrhythmias in ER. Other indirect factors increasing risk are AKI and metabolic acidosis, due to shifting of electrolytes.

Troponin levels may be elevated in ER, and it is critical to consider the clinical context. Cardiac troponin T assays may cross-react with expressed skeletal muscle proteins, but there are no reports of such crossover for troponin I. Factors that increase the likelihood of elevated troponin levels include higher peak CK levels, sepsis, recreational drug use, and AKI. As previously discussed in the Annotations to Algorithm II, Note 2, endurance athletes can have troponin elevations that transiently exceed the 99th percentile upper reference limit (URL) by 10–20-fold. However, troponin elevation in isolation is not diagnostic of myocardial injury. Cardiology consultation is recommended in troponin elevation with clinical features of myocardial injury (i.e., chest pain, syncope, arrhythmia, hemodynamic compromise, injury or ischemia patterns on ECG, cardiac risk factors, or isolated troponin elevation >10× URL).

H. Symptom Management and Preventative Therapies

Acetaminophen is the preferred analgesic to manage myalgia in ER. Patients who have transaminitis associated with ER can safely use acetaminophen, as the transaminitis is present from muscle injury instead of hepatocellular injury. If the transaminitis is atypical or if additional liver function tests are abnormal, the recommendation should be not to exceed 2 g/d. This guidance is based on the American Association for the Study of Liver Disease guidance.[72]

Opiates should be used on a limited basis for severe pain. All NSAIDs should be avoided for all patients with ER, even in patients without AKI.

The application of cryotherapy may be reasonable to provide short-term pain reduction within the first 24–72 hours. However, there is no evidence for the use of heat therapy, thus it is not recommended in the acute phase as it can worsen inflammation and edema.

There currently is no evidence to demonstrate that rest improves or accelerates recovery of ER. Ambulation is generally recommended as tolerated when not limited by pain, but resistance exercise should be avoided in the acute phase of ER.

6. Hospital Discharge Considerations

Limited evidence is available to guide discharge after CK levels start downtrending and clinical symptoms improve. In a series of 30 active-duty Service Members hospitalized for ER, mean CK level for discharge was 23,865 IU/L, with a wide range (1,410–94,665 IU/L). Twenty-nine of the 30 patients were discharged after CK levels started to downtrend. There were no adverse events or hospital readmissions in this study. A declining CK level is only one parameter to consider when deciding to discharge patients admitted for ER.[73]

To ensure safe discharge from the hospital, we recommend the following protocol. After admission and appropriate treatment, discharge may be considered when the following criterial are met:

- Demonstrated downtrending CK level
- Improvement of symptoms
- Correction of acid-base metabolic abnormalities
- Improving or resolved AKI
- A reliable plan for continued follow-up and profiling

There is no definitive CK level that establishes when a patient with ER may be discontinued from IV fluid therapy and safely discharged.[73, 74] The 2020 ER CPG from this consensus group identified that when CK levels fall below 32,000 IU/L* IV fluids could be safely discontinued and a trial of oral fluids may commence.[15] *Clinical experience with this recommendation has led to an amendment in this 2025 ER CPG.*

We recommend that patients with ER be managed initially with IV fluids until adequate urine output and peak CK levels have been achieved. Once CK levels begin to decline, patients may be transitioned to oral fluid intake, with a saline lock IV maintained. If CK levels continue to fall with oral fluid intake, renal function is stable or improving, and clinical symptoms are resolving, hospital discharge can be safely considered. As always, this CPG should be applied in conjunction with clinician judgment and appropriate follow-up.

Upon discharge, recurrence risk stratification should be performed. Consider specialty consultation for duty im-

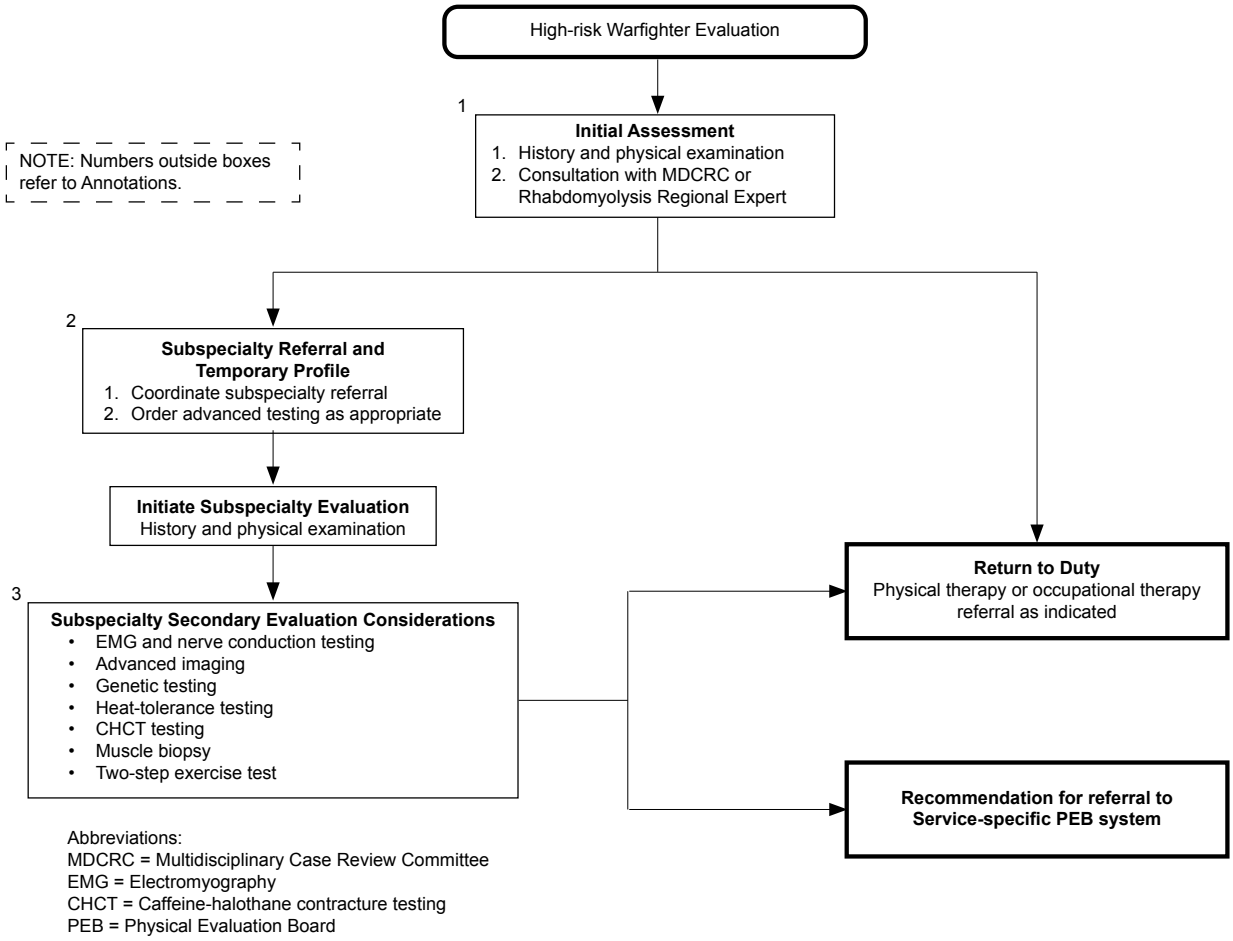
plications and MEB consideration. After discharge, the post-discharge follow-up and profiling should address the patient's clinical condition and any comorbidities. ER patients whose serum creatinine values return to baseline may still be at risk for repeated AKI episodes as long as approximately 6 weeks after the event, especially in a setting of dehydration or nephrotoxin exposure.

7. Proceed to Annotation 14, Algorithm I

A very common nephrotoxin is radiologic IV contrast. Patients who have experienced a recent episode of ER should receive fluid (NS or bicarbonate) and acetylcysteine prophylaxis for prevention of contrast-induced nephropathy, even if their serum creatinine has returned to "normal."[75, 76] NSAIDs should not be recommended after ER AKI, particularly in the recovery phase or in patients with severe AKI or requiring RRT. In these cases, nephrology recommendations should be considered for the avoidance durations for NSAIDs. Any ER patient whose renal function has not returned to baseline level after 2 weeks should be referred to nephrology. Clinicians can contact nephrology at any time by emailing their Surgeons General specialty advisor for nephrology.

*The clinician should also be aware of laboratory reporting criteria for CK levels. For example, at one MTF, CK levels were diluted 2×, and exact levels >32,000 were not reported unless specifically requested. Therefore, this protocol uses a 32,000 cutoff as the criterion to discontinue IV fluids. Check with local MTF about reporting criteria for CK levels before using specific numbers for transition to oral hydration.

SECTION 6: HIGH-RISK WARFIGHTER ADVANCED EVALUATION – ALGORITHM III



Algorithm III. Diagnostic Evaluation of the High-Risk Warfighter with a History of Exertional Rhabdomyolysis

Annotations to Algorithm III

1. Initial Assessment of High-risk Warfighter

If a review of a Warfighter's medical history and physical examination shows that they are at high risk for recurrent ER, consult a regional rhabdomyolysis expert. Consultants can be facilitated through contact with the CHAMP Warrior Heat- and Exertion-Related Events Collaborative (WHEC; https://www.hprc-online.org/resources-partners/whec). Contact WHEC using HPRC's Ask the Expert feature (https://www.hprc-online.org/ask-the-expert). To make sure you reach the appropriate experts, please include "WHEC" in the subject line of your email. Cases may be referred to WHEC's Multidisciplinary Case Review Committee (MDCRC) for further review and guidance.[28] Based on the consultation, the Warfighter may either be returned to duty or placed on temporary profile for further evaluation. The current MDCRC advanced evaluation approach is illustrated in Figure 3.

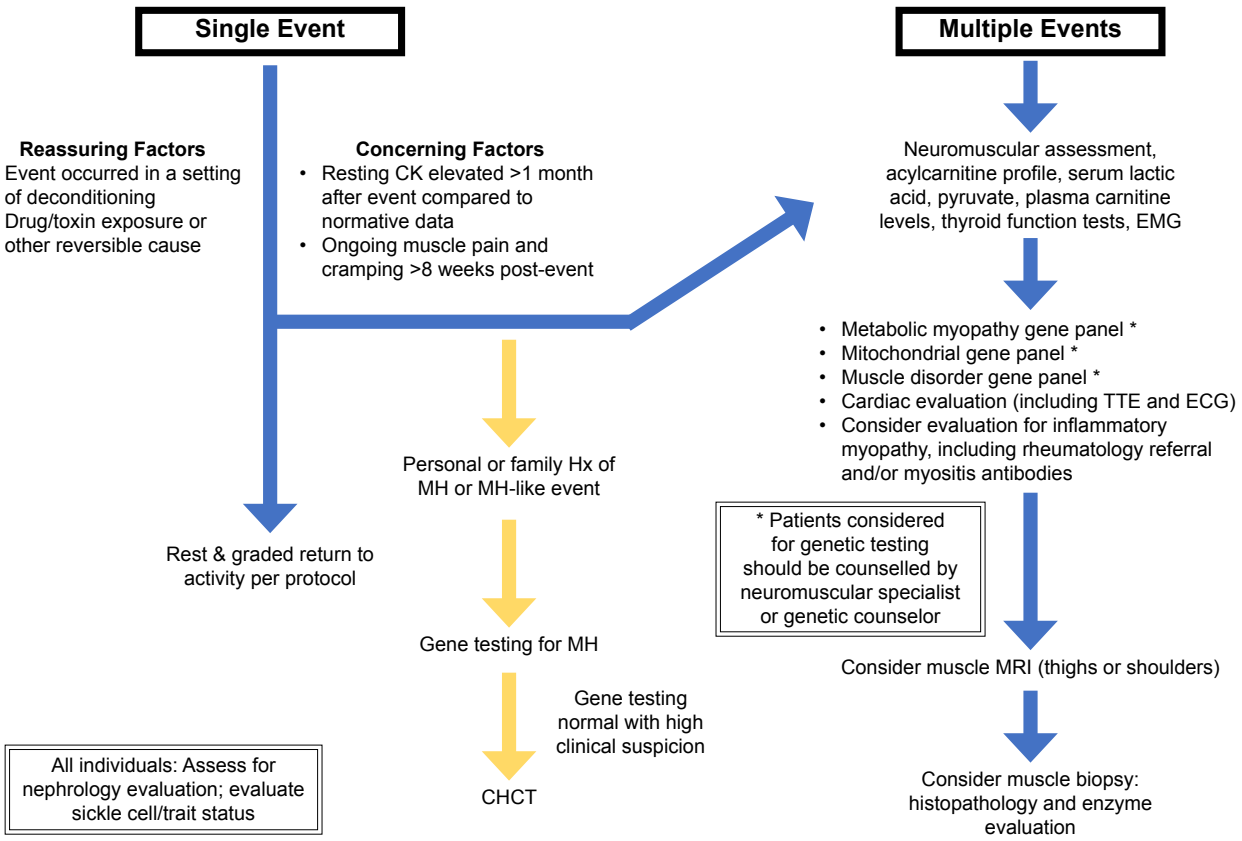


Figure 3. CHAMP WHEC MDCRC Advanced Evaluation Construct of Exertional Rhabdomolysis 2025

2. Subspecialty Referral and Temporary Profile

Coordinate with a subspecialty consultant for initial order of advanced testing and on-site referral evaluation, as appropriate. Initial testing may include any of the following serum tests to help rule out metabolic myopathic conditions (Figure 3):[77-79]

- Serum lactic acid
- Pyruvate
- Plasma carnitine
- Plasma acylcarnitine profile
- Thyroid function tests
- Electromyography (EMG)

3. Subspecialty Evaluation

Subspecialty testing will be synchronized by the tertiary care clinician. Testing may include multiple tests dependent upon the clinical presentation, including, but not limited to, EMG and nerve conduction studies, advanced genomic testing, muscle biopsy, and/or heat-tolerance testing.[79] In addition to laboratory testing, consultation with clinically indicated subspecialist(s)—hematology, nephrology, pulmonology, rheumatology, orthopedics, sports medicine, anesthesiology, or cardiology—may be requested. Several of the tests utilized to assess for underlying myopathic or mitochondrial conditions are further described below.

- **Genetic Testing.** With the advent of widely available next-generation sequencing, gene testing for high-risk recurrent rhabdomyolysis cases has taken a primary role.[78] Testing may include metabolic myopathy, mitochondrial, and muscle disorder gene panels. Whole exome or whole genome sequencing (see Glossary) may be considered as an alternative to a myopathy gene testing panel.
- **Caffeine-Halothane Contracture Testing (CHCT).** CHCT is performed using a muscle biopsy specimen to detect malignant hyperthermia. Patients who carry the MH gene may also be susceptible to ER. Under a non-triggering

anesthetic, surgeons excise a significant amount of muscle, often from the left vastus lateralis. From the muscle sample, six fresh muscle biopsy strips roughly the width of the patient's pinky and roughly 5 cm in length are prepared for exposure to caffeine and halothane solutions, where they are observed for increases in baseline and twitch contraction tension.

Malignant hyperthermia (MH) is a rare life-threatening condition triggered by exposure to succinylcholine or halogenated anesthesia gas (desflurane, sevoflurane, and isoflurane are the three in use in the United States today). MH, a dominantly inherited disease, causes hypermetabolism, skeletal muscle damage, hyperthermia, and most often death if untreated. The underlying physiologic mechanism is abnormal handling of intracellular calcium by the ryanodine receptor. Left untreated, the likelihood of organ failure and potential death is 80% during a MH episode.

The CHCT test should be considered for those who are suspected to be at significant risk for MH, either by family history, signs of an episode of MH (see Glossary), or any abnormal characteristics during anesthesia. For a patient to proceed with CHCT testing, a physician should first perform an ER evaluation. An ER evaluation may include a lipid panel, thyroid panel, standard electrolytes and chemistries, Exercise Intolerance Panel, Myoglobinuria Test Panel, high-recurrent CK levels, and recurrent MH episodes.

To discuss a potential clinical test, please contact mhlab@usuhs.edu. The MH consultant will guide you and/or the patient through testing options, records review, and the MH workup in general.

- **Advanced Cardiology Testing.** ER often results in complex MDCRC discussions exploring Warfighter exercise intolerance. Advanced cardiac evaluation (including transthoracic echo and ECG) may be directed to explore the cardiac contribution to the Warfighter's clinical presentation. Potential additional testing may include, but not be limited to: cardiopulmonary exercise testing (CPET), ECG and echocardiography, cardiac biomarker and genetic testing, and cardiac advanced imaging to include cardiac MRI. MDCRC will assist in guiding and facilitating advanced testing.
- **Forearm Exercise Testing.** Forearm exercise testing is no longer standard in the evaluation of potential metabolic myopathies. It can be used to identify biochemical evidence of glycogen storage diseases. Its use is generally reserved for the adjudication of variants of undetermined significance in genes related to glycogenolysis. If performed, a tourniquet should not be used. Ischemic conditions do not increase the diagnostic yield, but do increase the risk of rhabdomyolysis and compartment syndrome.
- **Two-Step Exercise Test.** The step test includes stepping up/down two stairs (30 cm height each) for 5 minutes at a set pace (54 steps/min by using a metronome) followed by 15 double leg squats completed in one minute (3 sec count down, 2 sec count up). A backpack weighted at 30% of bodyweight is worn during the tests, and blood samples are taken before, immediately after, and 48 and 72 hours after completing the exercise. Participants will be considered high responders if their exercise-induced increase in CK from baseline is >230 IU/L. Participants are asked to avoid exercise for ≥48 hours before the test. The Two-Step Exercise Test is currently utilized only as a clinical research tool.

SECTION 7: GLOSSARY

Acute kidney injury (AKI). AKI, also known as acute renal failure, is a sudden and rapid decline in kidney function, occurring over hours to days. It is characterized by the kidneys' inability to adequately filter waste and maintain proper fluid and electrolyte balance in the body. The Kidney Disease: Improving Global Outcomes (KDIGO) definition and staging system is the preferred definition. The KDIGO guidelines define AKI as follows:

- Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours, or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or
- Urine volume <0.5 mL/kg/hour for six hours.

Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE). ALPE, or acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise, is a relatively newly recognized condition characterized by severe loin or abdominal pain, nausea, and vomiting, accompanied by acute kidney injury without myoglobinuria (see Myoglobin below). It is often misdiagnosed as kidney stones or gastroenteritis due to its sudden onset in young men after vigorous exercise. Details are discussed in Algorithm I Annotation 7.

Compartment syndrome. Compartment syndrome occurs when tissue pressure from swelling muscle within a closed compartment exceeds the perfusion pressure and results in muscle and nerve ischemia. Acute compartment syndrome is a surgical emergency characterized by a rapid increase in pressure within a muscle compartment, often due to trauma, leading to potential nerve and muscle damage if not treated promptly with fasciotomy. In contrast, chronic compartment syndrome, also known as exertional compartment syndrome, is a condition typically caused by repetitive exercise, where pressure rises during activity and subsides with rest, and is usually not a surgical emergency. Compartment syndrome is frequently diagnosed with the five "Ps": pain, pallor, paresthesia, paralysis, and pulselessness.

Creatine kinase. CK, also known as creatine phosphokinase (CPK), is an enzyme found in the heart, brain, and skeletal muscles. It plays a crucial role in energy production by catalyzing the conversion of creatine and adenosine triphosphate (ATP) to phosphocreatine and adenosine diphosphate (ADP). Elevated CK levels in the blood can indicate muscle or heart damage.

Delayed onset muscle soreness (DOMS). DOMS is characterized by muscle soreness after physical exercise, typically occurring 24–72 hours after strenuous, prolonged, or non-familiar exercise training. It is thought to be due to processes involving extracellular muscle structures. For more information, including symptoms, see Algorithm I Annotation 1.

Exercise collapse associated with sickle cell trait (ECAST). ECAST is a rare but potentially fatal condition that can occur during strenuous exercise in individuals with sickle cell trait (SCT; see below). It is characterized by a sudden collapse during or after intense physical activity, often accompanied by muscle weakness, pain, and/or cramping. While SCT is generally considered benign, ECAST highlights a serious risk associated with intense physical exertion (see Algorithm I Annotation 11).

Exertional heat illness. EHI refers to a spectrum of conditions caused by the body's inability to regulate its temperature during physical exertion, especially in hot environments. It encompasses heat exhaustion (HE), exertional heat injury (EHI), and the more severe exertional heat stroke (EHS). For detailed information, see the 2024 CHAMP Clinical Practice Guideline for the Prevention, Diagnosis, and Management of Exertional Heat Illness.[2]

Exertional heat stroke. EHS is a serious, potentially life-threatening medical emergency characterized by a dangerously high core body temperature (usually above 40°C or 104°F) and central nervous system dysfunction, often occurring during strenuous physical activity.

Hyperkalemia. Hyperkalemia is a condition in which there is too much potassium in the blood. Mild hyperkalemia may be asymptomatic, but severe cases can cause progressive muscle weakness and potentially fatal arrythmias. Hyperkalemia and rhabdomyolysis are closely linked, with rhabdomyolysis often leading to hyperkalemia, a potentially dan-

gerous condition characterized by high potassium levels in the blood. Rhabdomyolysis, the breakdown of muscle tissue, releases intracellular contents, including potassium, into the bloodstream, causing elevated potassium levels. This can be further exacerbated by acute kidney injury, a common complication of rhabdomyolysis, which impairs the kidneys' ability to excrete potassium.

Lactic acidosis. Acidosis is a condition where there is too much acid in the body fluids, leading to a lower-than-normal blood pH. Lactic acidosis is a condition characterized by a buildup of lactic acid in the bloodstream, leading to a decrease in blood pH (acidosis). Lactic acid is a byproduct of cellular metabolism, specifically anaerobic glycolysis. Exertional rhabdomyolysis (ER) and lactic acidosis are related conditions where muscle damage from overexertion leads to the breakdown of muscle tissue and the release of harmful substances into the bloodstream. This can cause a buildup of lactic acid and other metabolic byproducts, potentially leading to serious complications such as acute kidney injury.

Malignant hyperthermia (MH). MH is a dominantly inherited disease resulting in risk of hypermetabolism, skeletal muscle damage, and death triggered by exposure to succinylcholine or halogenated anesthetic gas. In the operating room the following signs and symptoms are observed: early signs include muscle rigidity, especially in the jaw (masseter muscle spasm), rapid heart rate (tachycardia), rapid breathing (tachypnea), and a sudden increase in exhaled carbon dioxide (end-tidal CO_2) with a rapid rise in body temperature (hyperthermia) occurring as a later sign. Mutations causing MH susceptibility are often associated with muscle pain and cramping with or without exertional rhabdomyolysis. MH and exertional rhabdomyolysis, while two distinct conditions, both affect skeletal muscle, and have different triggers and mechanisms. While they are distinct, there is evidence suggesting a link between ER and MH susceptibility, with some individuals experiencing both conditions.

McMahon Score. This is a validated tool for predicting the risk of (1) AKI requiring renal replacement therapy and (2) death in the setting of rhabdomyolysis. The score identifies a low-risk population who are unlikely to have severe adverse outcomes, including AKI, as a result of the injury; <6 indicates a low risk of acute kidney injury or dialysis, while ≥6 indicates a higher risk of acute kidney injury or dialysis.

Metabolic acidosis. Acidosis is a condition where there is too much acid in the body fluids, leading to a lower-than-normal blood pH. Metabolic acidosis is a condition where there is too much acid in the body fluids, specifically the blood. It is characterized by a decrease in blood pH and bicarbonate levels, indicating a disruption in the body's acid-base balance. Metabolic acidosis is a common complication of rhabdomyolysis, a condition where damaged muscle tissue releases its contents into the bloodstream. This occurs because the breakdown of muscle cells releases substances such as potassium, phosphate, and myoglobin, as well as lactic acid, which contribute to the acidic state in the blood.

Metabolic myopathy. Metabolic myopathies comprise a clinically and etiologically diverse group of disorders caused by defects in cellular energy metabolism, including the breakdown of carbohydrates and fatty acids to generate adenosine triphosphate, predominantly through mitochondrial oxidative phosphorylation. Accordingly, the three main categories of metabolic myopathies are glycogen storage diseases, fatty acid oxidation defects, and mitochondrial disorders due to respiratory chain impairment.

Myalgia. Myalgia, also known as muscle pain or muscle aches, is a common symptom characterized by discomfort, soreness, and/or pain in the muscles. It can range from mild and temporary to severe and chronic. It can be caused by various factors, including injuries, infections, and certain medical conditions, e.g., delayed onset muscle soreness (DOMS), polymyalgia rheumatica, and fibromyalgia.

Myoglobin. Myoglobin is an iron- and oxygen-binding protein found primarily in muscle tissue, including cardiac and skeletal muscles. It acts as an oxygen storage unit, facilitating delivery of oxygen to working muscles and contributing to the red color of meat. Myoglobin is similar to hemoglobin but has a higher oxygen affinity and lacks the cooperative binding seen in hemoglobin. Rhabdomyolysis releases myoglobin into the bloodstream and urine (myoglobinuria), and can then cause acute kidney injury if present in high concentrations.

Myopathy. Myopathy refers to a group of diseases that primarily affect the muscles, causing weakness and potential wasting of muscle tissue. These disorders can be either inherited or acquired, with symptoms ranging from mild muscle fatigue to severe muscle weakness and potential involvement of other or-

gans. Myalgia and myopathy are related terms that are commonly confused. Myalgia refers to muscle pain, while myopathy is a broader term encompassing any disease or abnormality of the muscles. Myalgia can be a symptom of various conditions, including myopathies, but it can also be caused by other factors such as injury, overuse, or infection. Myopathy, on the other hand, refers to a disease process affecting the muscles themselves, potentially leading to symptoms such as muscle weakness, pain, and even muscle damage.

Myositis. Myositis refers to a group of conditions characterized by inflammation of the muscles, leading to weakness, pain, and fatigue. Several types exist, including dermatomyositis, polymyositis, and inclusion body myositis, each with its own unique characteristics. While the exact cause is not always clear, autoimmune responses, infections, and genetic factors are often implicated.

Rhabdomyolysis, exertional (ER). ER is an abnormal, excessive breakdown of skeletal muscle cells in the setting of a proximate, significant exercise history, characterized by severe muscle symptoms (pain, stiffness, and/or weakness) AND laboratory evidence of myonecrosis (CK level ≥5,000 IU/L and/or myoglobinuria).

Sickle cell trait (SCT). SCT is a genetic condition in which someone inherits one sickle cell gene and one normal gene. It is different from sickle cell disease (SCD), which requires inheriting two sickle cell genes. SCD is characterized by a single nucleotide mutation (adenine for thymine) in the β-globin gene that leads to the presence of sickle hemoglobin (HbS) resulting from the substitution of the amino acid glutamic acid with valine at the sixth position of the β-globin chain. While individuals with two βS-globin alleles (SCD) may develop severe clinical complications, people who inherit one sickle cell gene and one normal gene are identified as having SCT, and are considered to be largely benign, in addition to being partially protected from severe malaria. Approximately 300 million people worldwide and nearly 9% of African Americans in the United States (~3 million individuals) have SCT.

Transaminitis. Transaminitis, also known as hypertransaminasemia or elevated liver enzymes (transaminases), refers to a condition where the levels of liver enzymes are higher than normal in the blood. It is not a disease itself, but rather a sign that the liver is damaged or inflamed. Transaminitis can be linked to muscle issues in several ways. While transaminases are primarily associated with liver function, they are also found in significant amounts in muscle tissue. Therefore, muscle damage or disease can lead to elevated transaminase levels, specifically aspartate aminotransferase (AST) and, to a lesser extent, alanine aminotransferase (ALT). There is evidence of a diurnal variation in serum ALT, which may even vary day-to-day and may be affected by muscle injury or exercise. Muscle has more AST and ALT when compared with that in the liver because of a larger tissue mass. See Algorithm II Annotation 4B for further discussion.

Troponin. Troponin is a protein found in muscle cells of the heart. When heart muscle is damaged, troponin is released into the bloodstream, and higher levels in the blood indicate more heart muscle injury. Troponin testing—specifically, measuring the levels of troponin I and troponin T—is a key diagnostic tool for myocardial infarction and other heart conditions. Elevated cardiac troponin levels, however, can occur in the absence of acute coronary syndrome (ACS) or myocardial infarction. These non-ACS elevations can be caused by various conditions, including pulmonary embolism, sepsis, heart failure, renal failure, myocarditis, and even strenuous exercise. While troponin elevation indicates myocardial injury, it does not always signify a heart attack. An elevated troponin level may represent minor cardiac injuries or an inherent flaw of the assay that may identify cross-reactions with skeletal muscle proteins. Caution is advised in interpreting troponin elevations.

Whole exome sequencing (WES). WES is a genetic test that sequences all the exomes (protein-coding regions) of a person's DNA. It is a comprehensive genetic test that aims to identify genetic variants that may be causing or contributing to a person's health conditions.

Whole genome sequencing (WGS). WGS is a laboratory process that determines the complete DNA sequence of a person's genome. It provides a comprehensive view of an individual's genetic makeup, including both protein-coding and non-coding regions.

SECTION 8: APPENDICES

Appendix 1. Profile and Return-to-duty Guidance Considerations for Significant Delayed Onset Muscle Soreness and Low-risk Warfighters with Exertional Rhabdomyolysis

Note: No specific rehabilitation protocol can be proposed based on published data. The authors of this CPG recommend that the Warfighter should not return to full duty until there is evidence of clinical recovery (normal range of motion, the absence of myalgia, near normal recovery of strength, downtrending CK levels, and a normal UA). The following provides general recommendations suitable for those who screen as low risk. Those who screen as high risk per Annotation 14 (risk stratification) of Algorithm I require a more individualized approach. Clinical judgment and experience guide the return-to-duty process.

Phase 1

- Strict light indoor duty for 72 hours and encourage oral fluid intake.
- No weight training.
- Must sleep 7–8 consecutive hours nightly.
- Must follow up in 24–72 hours for repeat CK and UA testing.
- Transition to Phase 2 may be considered if the Warfighter is demonstrating clinical improvement at 24–72 hr, with improved range of motion, decreased myalgia, CK <5,000 IU/L and/or downtrending, and a normal UA.
- If CK value at 24–72 hours follow-up is ≥5,000 IU/L and/or UA is positive for blood with no RBCs, the Warfighter needs to be considered for high-risk markers and inpatient versus continued outpatient follow-up. If the clinician continues with outpatient management, the Warfighter should continue Phase 1 as delineated above, and be reassessed in 24–72 hours with repeat CK, creatinine, and UA, per clinical judgment. Once CK is clearly downtrending on repeat labs, continued lab testing is not warranted unless symptoms re-appear.
- Phase 2 may begin when there is evidence of clinical improvement with CK downtrending and normal UA. Otherwise remain in Phase 1 and return every 72 hours for repeat clinical assessment, to include CK/UA, until the criteria above are met.
- If CK remains ≥5,000 IU/L and/or UA is persistently abnormal for 2 weeks after injury or hospitalization, refer for expert consultation.

Phase 2

- The Warfighter may begin light outdoor duty, with no maximal effort or timed aerobic events.
- Light resistance training may commence, but avoid training to muscle failure.
- Ideally, Warfighter return to activity is guided and supervised (i.e., physical therapy, athletic trainer) as physical exertion, duration, and resistance progress from light to moderate (this process may take 3–4 weeks).
- Follow up with primary care clinician or aid station weekly.
- The Warfighter may transition to Phase 3 if clinical symptoms do not return and they show clinical recovery, including near-normal strength. Otherwise remain in Phase 2 and return at one-week intervals, when CK and UA repeat testing may be considered. May progress to Phase 3 when there is no significant muscle weakness, swelling, pain, or soreness. If myalgia persists without objective findings beyond 4 weeks, consider specialty evaluation to include psychiatry.

Phase 3 (Return to Duty)

- Return to regular outdoor duty and physical training.
- Follow up with care clinician as needed or if symptoms return.

Appendix 2. Coding of Exertional Rhabdomyolysis in Warfighters

A diagnosis consistent with ER should be coded as: physiologic muscle breakdown (ICD-10: M62.9 – Disorder of muscle, unspecified), exertional rhabdomyolysis (ICD-10: M62.82 – Rhabdomyolysis), or other causes for cola-colored urine such as exercise-induced hemolysis. Additional ICD-10 Y "cause" coding can be considered as appropriate; such actions will assist with future epidemiologic efforts:

a. Y92.13 Military base as the place of occurrence of the external cause
b. Y37.90XA Military operations, unspecified
c. X50.0 Overexertion from strenuous movement or load (lifting weights)
d. Y93.02 Activity – running

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