Clinical Practice Guideline for the Management of Exertional Rhabdomyolysis in Warfighters 2020

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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 (CK level ≥5X ULN) in the setting of recent exercise.

Contributing factors: High-intensity, repetitive, and/or prolonged exercise unmatched to fitness level; dietary supplement use (especially stimulants); hot and humid climate; genetic factors (sickle cell trait, disorders of lipid or glycogen metabolism, etc.).

High-risk markers:

- CK >20,000 U/L
- Suspicion for potential compartment syndrome
- Acute kidney injury (See KDIGO criteria)
- Metabolic abnormality (e.g., hyperkalemia, hyperphosphatemia, acidosis)
- Sickle cell trait carrier
- Limited patient follow-up (e.g., trainee lives alone)

Outpatient treatment criteria: ER patients with no high-risk markers (see above) generally may be treated as outpatients. Outpatient treatment in such patients consists of oral rehydration, limited physical activity, and close follow-up (often every 24 hours-72 hours in early stages).

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

Inpatient discharge considerations: After admission and appropriate treatment, discharge may be considered after demonstrating down-trending CKs, improving symptoms, improving or improved AKI and metabolic abnormalities, and a reliable plan for continued follow up.

High risk of recurrence:

- Delayed clinical recovery (despite more than a week of activity restriction)
- Persistent CK elevation above 1,000 U/L, despite rest for at least 2 weeks
- ER complicated by AKI that does not return to baseline within 2 weeks
- ER after low to moderate workload
- ER complicated by drug or dietary supplement use
- CK peak >100,000 U/L
- Personal or family history of ER, recurrent muscle cramps or severe muscle pain, significant heat injury, sickle cell trait or disease, malignant hyperthermia, unexplained complications or death following general anesthesia

Additional Guidance for Clinicians:

- Serum CK is “gold standard” for diagnosis and monitoring of ER; serum myoglobin is best used for risk prediction
- CK >5X ULN is a low threshold designed for high sensitivity, however it has low specificity. Normal baseline and post-exercise CK levels vary by age, gender, race, type of exercise, etc. Some experts recommend diagnostic threshold for ER in physically active people of CK >50X ULN for increased specificity

- Obtain and document a detailed history of supplement use in all cases of ER
- Do not use ICD-10 codes for rhabdomyolysis unless meeting ALL diagnostic criteria (severe muscle pain and tenderness, and CK >5X ULN), so as to not hinder research

Introduction

Exertional rhabdomyolysis (ER) is a condition frequently seen in the setting of military training and operations; it frequently occurs when the level of exertional stress is greater than the warfighter is accustomed.[1] This condition can be precipitated by a number of factors, often working in tandem, and is commonly co-morbid with exertional heat illness, in particular, heat stroke.

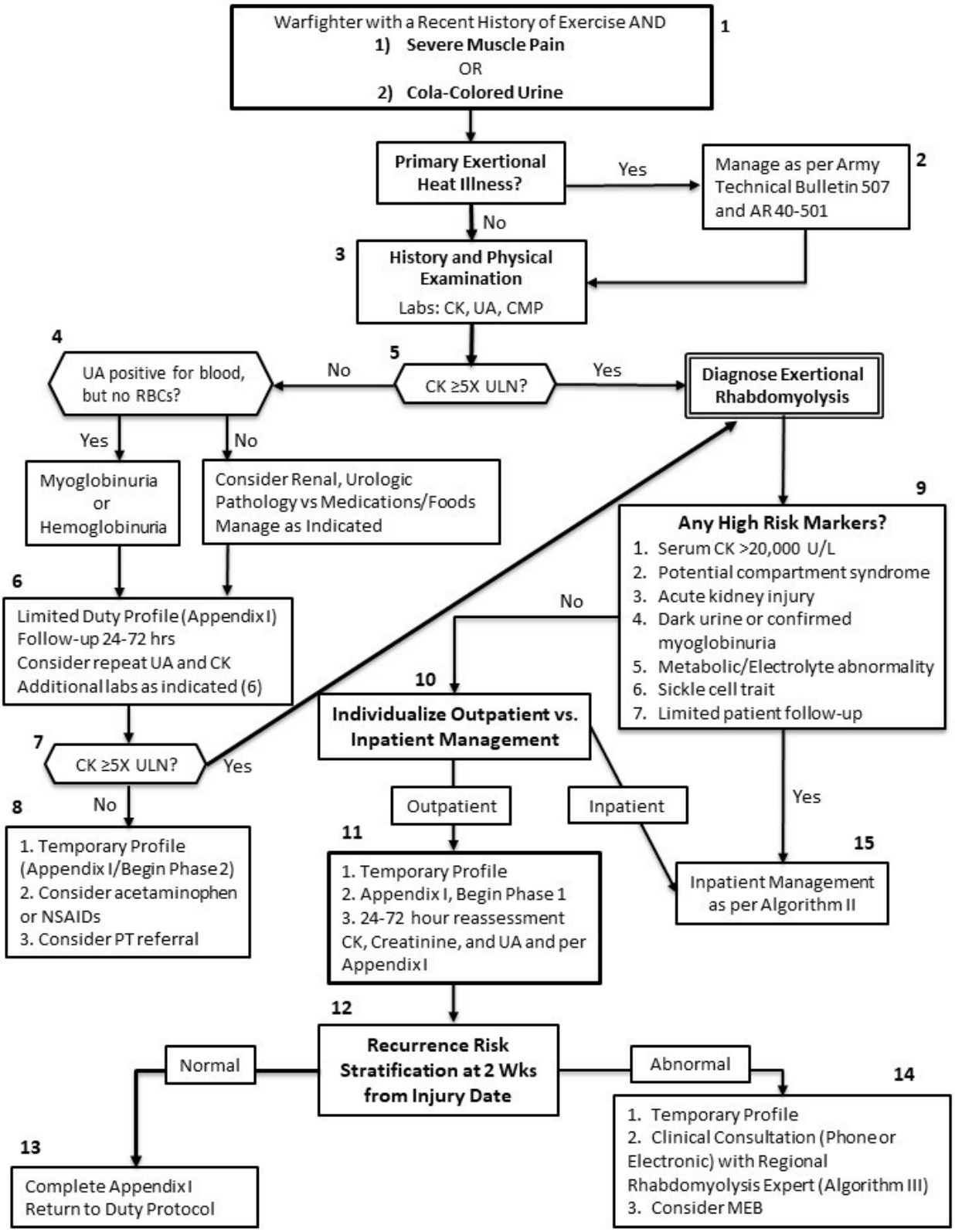
Although the majority of warfighters who experience ER recover and will be safely returned to duty, some may experience residual injury, while others may be at risk for future recurrences. These recurrences may limit the warfighter's effectiveness and potentially predispose to serious injury, including permanent disability, and death. Importantly, an untimely recurrence may compromise a unit's mission.

Military providers confronted by warfighters with ER can face challenging clinical decisions beyond the initial identification and management. These decisions include:

- Outpatient versus inpatient management;
- Hospital discharge criteria;
- Who can be safely returned to duty;
- How should a patient or warfighter be restricted/limited ("profiled");
- How long should the profile period be;
- Does the warfighter warrant further medical evaluation for an underlying disorder, e.g. a metabolic myopathy;
- Does the ER event warrant referral for a medical/physical evaluation board (MEB), which would help determine whether the event might permanently interfere with his or her ability to serve on active duty?

This consensus clinical practice guideline was constructed jointly within the U.S. Military to assist providers 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 profiles is included. Specific warfighter management questions can be directed to through an Ask-the-Expert function at https://www.hprc-online.org/ask-the-expert.

Algorithm I. How to stratify a warfighter with suspected exertional rhabdomyolysis



Annotations to Algorithm I

1. Post-Exercise Muscle Pain or Cola-Colored Urine. Muscle pain usually presents within the first 24 hours and peaks at 72 hours after strenuous, prolonged, or non-familiar exercise training, in particular after a significant amount of eccentric exercise (e.g., push-ups, pull-ups, squats, or participation in unaccustomed conditioning exercises). Delayed onset muscle soreness (DOMS) can be a symptom of physiologic muscle breakdown and is best described as muscles that become sore and stiff, usually one to three days after a bout of moderate to strenuous exercise. ER and DOMS can have overlapping symptoms, but key symptoms and findings of ER which help distinguish it from typical physiologic muscle breakdown and/or DOMS include:

- Pain and tenderness to palpation usually 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
- Persistent or worsening pain and soreness for more than 5-7 days after the precipitating activity.

It should be noted that 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, however the full differential diagnosis for dark urine must be considered. These warfighters should undergo the same initial diagnostic evaluation as an individual with a classic presentation of ER.

The clinician's judgment is critical to determine the severity of muscle pain and myonecrosis: in many cases, a creatine kinase (CK) level in excess of 5X the upper limit of normal (ULN) and other assessments (pain, urinary myoglobin) will trigger further evaluation and a clinical determination of the most effective and safest way to treat the warfighter. The ULN is defined by each laboratory, but is usually about 200 U/L. However, studies in both warfighters and athletes have demonstrated that high CK levels (up to 175X ULN) can be tolerated without any symptoms or evidence of acute kidney injury in some individuals, leading some experts to suggest a minimum CK laboratory threshold for ER in physically active individuals to 50X ULN for improved specificity.[2] It cannot be overemphasized that SYMPTOMS, co-morbidities (e.g. acute kidney injury), and clinical judgment should drive management.

2. Primary Exertional Heat Illness: Exertional rhabdomyolysis may be associated with the spectrum of exertional heat illness, including heat exhaustion, heat injury, and heat stroke. All are significant threats to military populations because of frequent occupational and strenuous physical activities in hot and humid environments. A recent revision of AR 40-501, Chapter 3-45 defines exertional heat illness categories as follows:[3]

- Heat Exhaustion: a syndrome of hyperthermia (core temperature at time of event usually ≤40°C or 104°F) with collapse or debilitation occurring during or immediately following exertion in the heat, with no more than minor central nervous system (CNS) dysfunction (headache, dizziness), which resolves rapidly with intervention.
- Heat Injury: heat exhaustion with clinical evidence of organ (e.g. liver, renal, gut) and/or muscle (e.g. rhabdomyolysis) damage without sufficient neurological

symptoms to be diagnosed as heat stroke.

- Heat Stroke (HS): a syndrome of hyperthermia (core temperature at time of event usually ≥40°C or 104°F), collapse or debilitation, and encephalopathy (delirium, stupor, coma) occurring during or immediately following exertion or significant heat exposure. HS is often complicated by systemic inflammatory activation, disseminated intravascular coagulation, and/or organ/tissue injury (e.g., rhabdomyolysis).

If the primary event is exertional heat illness, then the provider should exit this algorithm, and the patient initially managed appropriately as heat illness per details in the AR 40-501 and the military technical bulletin, Heat Stress Control and Heat Casualty Management (TB MED 507/AFPAM 48-152) (https://www.usuhs.edu/champ-provider).[3,4] Return to duty decisions will likely be dictated by the nature of the heat disorder.

3. History, Physical Examination and Diagnostic Testing. The medical provider should perform a focused history and physical examination to confirm a diagnosis consistent with 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:

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

The provider should specifically inquire about and document the use of medications (e.g. statins, antipsychotics, stimulants),[5] dietary supplements (e.g., performance enhancing, weight loss, muscle building, stimulant/caffeine-containing products), and energy drinks, as well as ask about current sleep patterns, nutritional habits, and whether a co-existent illness is present, as these are known contributors to ER.

If the history and examination render a different diagnosis, further evaluation and a work- up should be directed appropriately. Otherwise, the possibility of severe muscle injury should be evaluated at this point with a serum CK, blood chemistry profile (including potassium, bicarbonate, calcium, phosphorus, blood urea nitrogen [BUN] and creatinine), and a urinalysis (UA) with microscopic examination. Urine or serum myoglobin should be considered dependent upon military treatment facility resources. Current evidence suggests that while pathognomonic for muscle injury, serum myoglobin has low sensitivity and should not be utilized for the 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, however there are no data to support its application to patients with ER.[6,7]

4. Evaluating Patients with Dark or "Cola-Colored" Urine. Dark or "cola-colored" urine is relatively uncommon but may be observed with greater frequency following exercise. When evaluating patients presenting with dark urine, a thorough history and examination are critical as one considers the full differential diagnosis. While an onset of dark urine within 24 hours following a bout of strenuous exercise is highly suggestive of ER, other etiologies must also be considered.

After a history and exam, urinalysis with microscopy must be performed. When urine sediment is red or dark, the differential diagnosis includes hematuria due to glomerular, nonglomerular, 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). In cases of hematuria with red/dark sediment, the urinalysis should be repeated and, as indicated, the patient should be managed in consultation with a nephrologist or urologist. When the urine supernatant (top portion of a spun urine sample) is red or dark, one must consider hemoglobinuria (e.g., exercise-induced hemolysis), myoglobinuria (implies rhabdomyolysis), urine discoloration due to medications (e.g., phenazopyridine, rifampin, phenytoin), foods (e.g., beeturia, also blackberries, rhubarb, senna, food dyes), or porphyria (rare).

This algorithm includes branches for when the urinalysis is positive for blood in the absence of RBCs, which may represent myoglobinuria. It is possible, especially in the first 12 hours after strenuous exercise, that an individual will have a CK <5X ULN, but with myoglobinuria (myoglobin peaks before CK). In these cases, a CK and metabolic panel should be repeated in approximately 24 hours, and if CK ≥5X ULN, a diagnosis of ER is appropriate. As noted below (#5), the orthotoluidine portion of the dipstick turns blue in the presence of hemoglobin or myoglobin, so the differential diagnosis in these cases includes ER and exercise-induced hemolysis.

High-intensity or prolonged exercise often results in benign, self-limited hematuria or hemolysis. 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[6,8]. 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 ("footstrike hemolysis"). Similarly, exercise-induced hematuria is also common, but rarely presents as gross hematuria. Urinalysis with microscopy will reveal presence of variable quantities of intact RBCs. One recent 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[9,10]. 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.

5. Diagnosis and Prognosis of ER. Although ER is a pathologic condition (and is, by definition, symptomatic), muscle breakdown of a lower degree is also a normal result of strenuous exercise (DOMS).[11,12];[2] Whereas DOMS lasts only a few days and causes little disability, ER can be overwhelming and devastating, especially when associated with other variables such as dehydration, sickle cell trait, use of certain drugs, dietary supplements, caffeine or alcohol, excessive exercise, exertional heat illness, underlying genetic conditions, or other incompletely understood contributing factors. The potential devastating consequences of ER include compartment syndrome, renal failure, and death. Although uncommon, ER may reflect an underlying metabolic or myopathic process that predisposes the warfighter to severe and/or recurrent ER. Accordingly, significant clinical expertise is required when treating ER patients, evaluating potential complications from ER, and additionally 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.[13]

A diagnosis of ER is made when there are severe muscle pain symptoms 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), alanine aminotransferase (ALT) and/or hydroxybutyrate dehydrogenase. 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 exertional rhabdomyolysis is observed, such as severe muscle pain and weakness in the setting of recent strenuous exercise, then CK levels ≥5X ULN are accepted as evidence of significant muscle breakdown and generally considered consistent with a diagnosis of ER. The provider is reminded that CK elevations occur for many other reasons, such as inflammatory myopathies and muscular dystrophies, 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 exercise, can be used to diagnose ER.[6,7,11]

Myoglobin is theoretically the best 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 make or rule out a definitive diagnosis 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), however there are no data validating this application for patients with ER.[7,14]

Serum myoglobin is normally bound to plasma globulins and under healthy conditions only a small fraction reaches the glomeruli. Serum myoglobin is cleared rapidly by the kidney, with a half-life of 2-4 hours, maintaining a serum concentration of less than 3 μg/l.[7,15-17] In the face of severe muscle damage, blood levels of myoglobin overwhelm the binding capacity of the circulating proteins, so free myoglobin reaches the glomeruli and is filtered into the renal tubules. Elevations in serum myoglobin occur before a rise in serum CK, but the elimination kinetics of serum myoglobin are more rapid than that of CK, which makes the often evanescent rise in serum myoglobin a less reliable marker of muscle injury. Diagnostic tests for urine myoglobin are often not readily available, and it may take more than 24 hours to obtain results. However, urine screening for rhabdomyolysis may be performed by dipstick if the urine sediment is also examined. The orthotoluidine portion of the dipstick turns blue in the presence of hemoglobin or myoglobin, so if the urine sediment does not contain erythrocytes, the positive dipstick reading may reflect the presence of myoglobin in the appropriate clinical setting. Of note, 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)[8]. Therefore, a urinalysis positive for blood, with absence of RBC's in the sediment, is neither sensitive nor specific for ER. It may be noted that for field expedient analysis, the supernatant (top portion) of the spun urine sample will typically be brown in myoglobinuria and pink in hemoglobinuria. However, urine myoglobin is somewhat unstable, making supernatant color a fallible marker. Altogether, using any indirect marker of myoglobinuria to diagnose ER or predict ER-associated AKI remains inconclusive.[15-17]

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, gender and ethnic variation may contribute to unique baseline CK levels.[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.[20-26] Although the case definition for pathologic ER is somewhat controversial, this guideline utilizes the following to enter the management algorithm:

- SEVERE muscle pain (see above for symptoms) and
- Laboratory evidence of muscle injury (CK level ≥5X ULN)

CK >5X ULN is a low threshold designed for **high sensitivity**, however it has very **low specificity** for ER. Using this definition provides the greatest safety net in assisting the clinician in the initial work-up of this challenging syndrome. Because finding a CK ≥5X ULN is not uncommon in exercising warfighters (in particular African American warfighters who may have baseline CK of 600 U/L,[20,22,26] it important to emphasize that entry into this clinical algorithm requires the appropriate clinical picture, including severe muscle pain.

6. Management. The warfighter with a documented visit to the clinician with signs/symptoms consistent with DOMS (physiologic muscle breakdown: ICD-10: M62.9 – disorder of muscle, unspecified) should be placed on a temporary profile (https://www.usuhs.edu/champ-clinical-tools) with limited indoor duty for the rest of the day, no regular physical training, and a mandatory medical re-evaluation in 24-72 hours, with consideration for repeat UA and CK assessment. Oral rehydration should be encouraged (Appendix 1/Phase 1).

7. Urinalysis and CK. Patients who are initially diagnosed with DOMS (physiologic muscle breakdown; ICD-10: M62.9), as they do not meet the criteria for ER, should be reevaluated by a knowledgeable clinician within 24-72 hours. At this time, a repeat urinalysis and CK can be performed if clinically indicated (dark urine, no clinical improvement in pain). If the patient's symptoms have resolved, and the CK is <5X ULN, the warfighter may be gradually returned to duty as determined by the treating provider with guidance from Appendix 1. Any warfighter who demonstrates clinical signs of ER (severe muscle pain, stiffness, weakness) and tests positive for CK greater than 5X ULN should be diagnosed with ER and further evaluated for high-risk markers (See #9 below).

8. Temporary Limited Duty Profile. At the 24-72 hours follow-up, a warfighter diagnosed with physiologic muscle breakdown may continue on a limited duty profile for up to 72 hours, after which activities will be advanced as tolerated in accordance with the recommendations of Phase 2 of Appendix 1. (https://www.usuhs.edu/champ-clinical-tools). The provider 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. Additionally excessive doses of NSAIDs and/or acetaminophen can result in nephro- or hepatotoxicity, respectively.[27] This risk may be heightened following the stress of significant exertional muscle breakdown.

9. Screen for Initial "High Risk" Markers. 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 are presented in Table 1.

Currently, no clinical prediction rule exists for risk-stratifying patients with ER or for determining who will develop AKI.[28,29] Although a peak CK of >5,000 U/L is reported to be 55% specific and 83% sensitive for predicting AKI with traumatic rhabdomyolysis,[30,31] ER patients

with mild symptoms and serum CK levels ≤20,000 U/L are considered at low risk and may be treated as outpatients. Outpatient treatment in such patients consists of oral rehydration, limited physical activity, and careful follow-up. A CK >20,000 U/L should be considered a high-risk marker and triaged to a higher level of care for possible inpatient treatment.

ER can be associated with the development of acute compartment syndrome (ACS). ACS occurs when the tissue pressure within a closed muscle compartment (e.g., triceps, thigh) exceeds the perfusion pressure and results in muscle and nerve ischemia. Early signs of an ACS include severe pain worse 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. If only mild in degree, these abnormalities do not, in and of themselves, warrant admission, but do necessitate close follow-up at a minimum, with immediate access to laboratory 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.

The presence of any of the above "high risk" markers warrants triage/referral of the patient to a provider and/or setting familiar with the diagnosis and management of ER (e.g. neurologist, nephrologist, or sports medicine physician). This will likely include inpatient admission.

10. Individualize Outpatient Management: The warfighter diagnosed with ER, but without high risk markers, should be considered for outpatient management. There is significant controversy on 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 oral hydration may be reasonable for athletes with CK levels of 20,000-50,000 U/L and no additional high-risk features.[32,33] This guideline, however, recommends that in a military population, a CK level of 20,000 U/L or less without any high-risk features, and reliable patient follow-up should be considered for outpatient management. Warfighters should be encouraged to monitor urine output with a goal of approximately 200 ml per hour, 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, any evidence of complications, and should include a repeat blood draw for CK and basic metabolic panel. If CK continues to downtrend, renal function remains normal, 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, or increasing CK levels should prompt admission for management with IV fluids.

The decision to hospitalize the warfighter should be contingent upon factors such as metabolic abnormalities, acute kidney injury, social status (i.e. trainee, recruit, barracks dweller, and limited patient follow up), and CK level. The final decision for inpatient management rests on clinical judgment.

11. Profile and Follow-up. In regards to profiling, the warfighter should be placed on a limited duty profile that excludes field duty (e.g., extended marching, obstacle courses, and land navigation). It must also limit aerobic and anaerobic exercise per Appendix 1 recommendations

(Rhabdomyolysis- Low Risk Profile in the website parallels the Appendix 1 recommendations) (https://www.usuhs.edu/champ-clinical-tools). 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. When CK value is <5X ULN and the UA has returned to normal, the warfighter should begin a graduated return to duty protocol per Appendix 1. 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, as well as mitigation strategies as applicable.

12. Recurrence Risk Stratification at 2 weeks from Date of Injury. To define the case as "high risk" for recurrence, at least one of the following conditions must exist:[12]

- Delayed clinical recovery (despite more than a week of activity restriction)
- Persistent CK elevation above 1,000 U/L, despite rest for at least 2 weeks
- 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;
- Personal or family history of recurrent muscle cramps or severe muscle pain that interferes with activities of daily living or military performance;
- Personal or family history of malignant hyperthermia or family history of unexplained complications or death following general anesthesia;
- Personal or family history (if personal status unknown) of sickle cell disease or trait;
- ER complicated by drug or dietary supplement use
    - Drugs increasing risk for ER: Statins, antipsychotics (e.g., haloperidol), stimulants (amphetamines, methylphenidate)
    - Dietary supplements increasing risk for ER: Stimulants (e.g., caffeine, synephrine, octopamine, yohimbine, ephedra)
    - For a list of other stimulants in supplements see: http://hprc-online.org/dietary-supplements/files/stimulants-found-in-dietary-supplements-pdf stimulant
    - Although supplements do not imply a medical condition that would necessarily warrant a MEB or detailed work-up, individual as well as unit education may be warranted.
- Personal history of significant heat injury; or
- CK peak > 100,000 U/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 week (symptoms and exam findings normalized)
- All laboratory values normalized within 2 weeks with exercise restriction
- **At least one** of the following conditions must also exist:
    a. Physically trained warfighter with a history of very intense training;
    b. Known participation in extreme conditioning program prior to event
    c. No personal and family history of ER or previous reporting of exercise-induced severe muscle pain, muscle cramps, or heat injury;
    d. Existence of other ER cases in the same training unit;

e. Identifiable period of sleep and/or nutrition deficit;
f. Concomitant viral illness or other infectious disease.

13. Complete Appendix 1: Return to Duty Guidelines for Physiologic muscle breakdown and Low Risk Warfighters with Exertional Rhabdomyolysis**.**

14. Abnormal at Two Weeks after injury: If at 2 weeks after injury, clinical indicators (laboratory values, physical exam findings) remain abnormal, the warfighter should be referred to or discussed with an appropriate specialist (e.g. neurologist, nephrologist, sports medicine physician) or regional consultant for further management and potential evaluation for an underlying disorder that may predispose to recurrent injury https://www.usuhs.edu/mem/champ-provider. The evaluation may include, but not limited to: EMG, muscle biopsy, caffeine-halothane contracture test, genomic/proteomic testing, and/or exercise challenges (See Appendix 1). Return to duty and profiling are individualized based on results of testing and presented in Algorithm III.

15. Manage as per Algorithm II: Patients with CK levels >20,000 U/L or any significant high risk markers, may require further testing and observation[17,30,31,34] in an inpatient setting. Accordingly, higher level of care should be considered and the patient should be managed as per Algorithm II.

Appendix 1. Return to Duty Guidelines for Physiologic muscle breakdown and Low Risk Warfighters with Exertional Rhabdomyolysis

Phase 1:

- Strict light indoor duty for 72 hours and encourage oral hydration, salting of food;
- No weight training;
- Must sleep seven to eight consecutive hours nightly;
- Must remain in thermally controlled environment;
- Must follow-up in 24-72 hours for repeat CK/UA;
- If CK value at 24-72 hours continues to be <5X ULN and UA continues to be normal, Phase 2 may begin after the initial 72 hours of limited duty. (Physiologic Muscle Breakdown Profile)
- If CK value at 24-72 hours follow-up is >5X ULN and/or UA is positive for blood with no RBC's 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 is to continue on Phase 1 delineated above (Low Risk Rhabdomyolysis Profile) and followed in 24-72 hours with CK, creatinine and UA as per clinical judgment;
- When CK value is <5X ULN and UA has returned to normal, begin Phase 2. Otherwise remain in Phase 1 and return every 72 hours for repeat CK/UA until the criteria stated above are met;
- If CK remains >5X ULN and/or UA is persistently abnormal for 2 weeks after injury or hospitalization, refer for expert consultation.

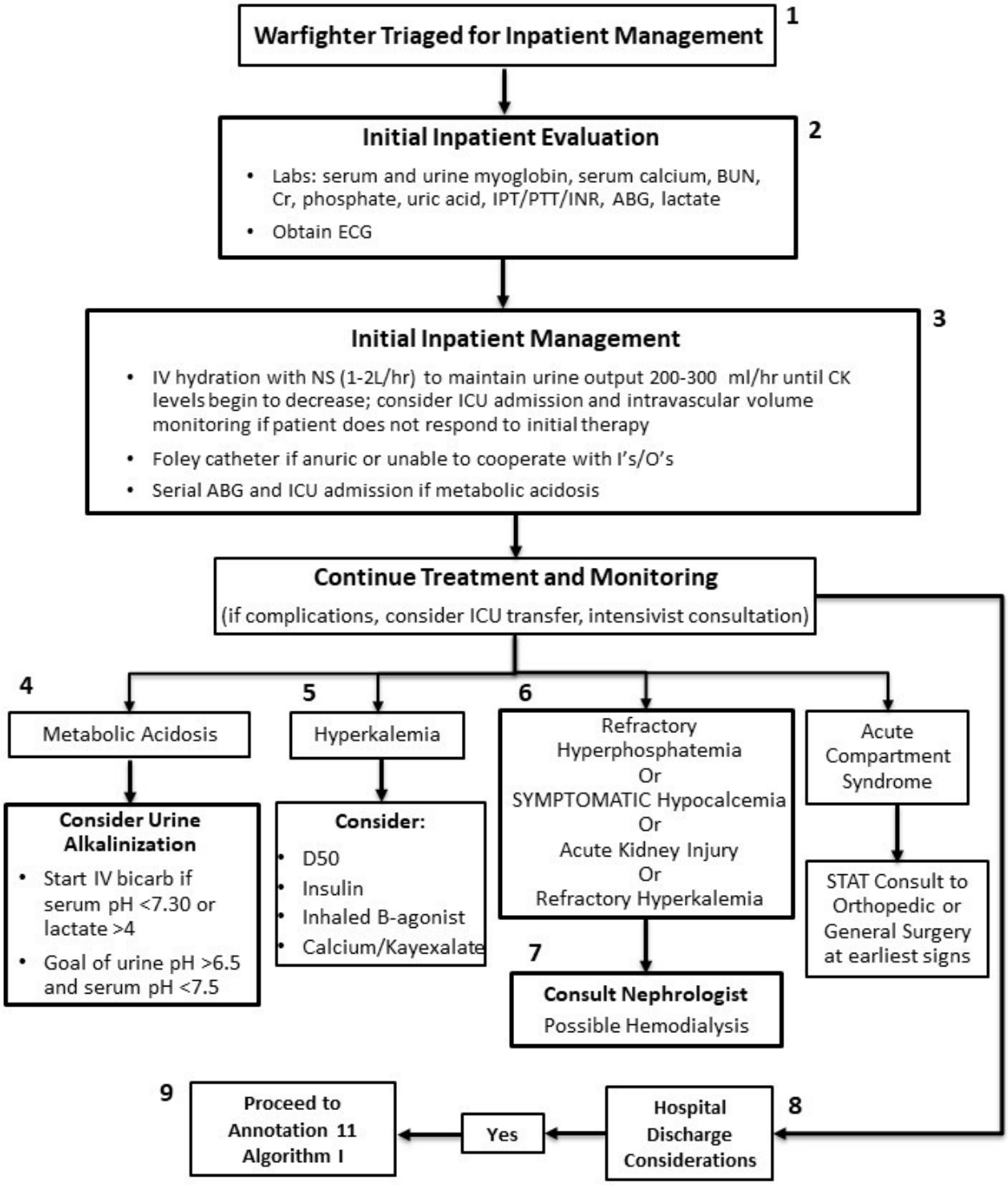
Phase 2:

- Begin light outdoor duty, no strenuous physical activities;
- Lightweight resistance training;
- Supervised (i.e., physical therapy, athletic trainer) physical activity at own pace and distance;
- Follow-up with care provider in one week;
- If clinical symptoms do not return, then begin Phase 3. Otherwise remain in Phase 2 and return at 1-week intervals. 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 regular outdoor duty and physical training;
- Follow-up with care provider as needed.

Algorithm II. Inpatient Management of Acute Exertional Rhabdomyolysis



Annotations to Algorithm II

1. Patient Referred for High Risk Markers. Review what high risk markers have resulted in the patient being referred to a higher level of care. These "high risk" markers (See Table 1) are a guide, and do not supersede clinical judgment.

2. Entry into Higher Level of Care. The facility should have the capability for additional laboratory evaluations, short-term observation and access to intravenous therapy. Further laboratory tests should include: serum and urine myoglobin, serum calcium, BUN, creatinine, phosphate, uric acid, PT/PTT/INR, and LFTs, if not already obtained. Of note, elevated transaminase levels in the setting of ER are expected, and generally result from myocyte release rather than hepatocellular damage. In addition, an ECG should be conducted to assist in the assessment and management of hyperkalemia.

Each and every case needs to be individualized when a decision for hospital admission is considered. The authors believe patients with any high-risk markers should be strongly considered for admitting an ER patient to the hospital, regardless of the CK value.

The decision for ICU admission is highly dependent on individual facility resources. That being stated, considerations for ICU admission include the need for invasive cardiopulmonary monitoring, and conditions that may prompt consideration for dialysis e.g. congestive heart failure, persistent hyperkalemia or persistent metabolic acidosis.

3. Hospital Admission: In ER patients who are admitted and have CK levels >20,000 U/L, aggressive intravenous fluid (IV) therapy with isotonic fluids (5% dextrose and 0.45 normal saline (NS), lactated Ringer's solution, or NS with or without bicarbonate)[17] should ideally be initiated with a target urine output of 200-300 ml/hr. 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 based urinary tract infection. In general, in otherwise young, healthy warfighters, ER generally responds well to IV hydration alone without need for alkalization. Fluid volumes can range from 400 mL/hr, 20 mL/kg in the first 24 hours, to 4 to 8 L per day,[17] but at a rate resulting in a urine output of 200-300 mL/hr[34] until CK levels begin to decrease. Large volumes of normal saline can contribute to hypernatremia and hyperchloremia and therefore after initial management, we recommend switching fluids to 0.45 normal (NS). If the patient does not respond to initial IV fluid therapy, a clinical consultation with the appropriate specialist should be sought. In addition, when fluid resuscitation fails to correct intractable hyperkalemia and acidosis, nephrology consultation for dialysis should be considered.

Treatment of the warfighter with ER is focused on preventing complications, and is guided by continual assessment of vital signs, serial physical examinations, laboratories, and urine output. Peak CK levels are generally reached within 2 to 3 days. Although no validated hydration algorithms have been established, IV fluid therapy is generally not discontinued until CK and creatinine levels are decreasing, and urine output is adequate, 200-300ml/hr).

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 hydration and the warfighter must be evaluated periodically for dyspnea, rales and evidence of fluid overload. Furosemide may alleviate

pulmonary edema and should be considered in that setting. Minimally invasive and invasive techniques, if utilized for volume assessment and management, should be performed under the direction of a critical care intensivist.

No evidence exists as to whether rest improves or accelerates recovery, although ambulation is generally recommended as tolerated and when not limited by pain. Pain should be controlled with acetaminophen and very limited use of opiates. NSAIDs should be avoided and CK followed (drawn periodically, q6-12 hours).

Acute compartment syndrome (ACS) is a well-described potential late complication[17,35] of ER. 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 on passive stretching of a muscle;
- Paresthesias 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 in excess of 30 mm Hg should prompt consideration for surgical fasciotomy, all management decisions are guided by the treating consultant.

4. Positive Urine Myoglobin or Metabolic Acidosis. Although no large, randomized trials suggest any clinical advantage to urine alkalinization over aggressive hydration for patients with ER, a recent retrospective review of 56 traumatic rhabdomyolysis patients with CK > 10,000 U/L suggests that a protocol of forced alkaline diuresis with mannitol and bicarbonate significantly decreases the odds for developing AKI (OR = 0.175).[36] However, the clinician needs to be cautious as alkalinization can potentially worsen hypocalcemia, and this study's results may not be generalizable to individuals with ER. If the decision is made to alkalinize the urine, the goal urine pH is >6.5 while maintaining serum pH <7.5.[28,36] This can be accomplished by administering 2 ampules of sodium bicarbonate diluted in one liter of D5W at a rate of 75-125 ml/hr. Monitor serum K^+, Ca^{++} and urine pH every 4 hours. Consider nephrology consultation if urine pH does not rise or serum Ca^{++} drops.

5. 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 the potassium is >6 MEq/dL.

6. Hypocalcemia and/or Hyperphosphatemia:

Hypocalcemia: Deposition of Ca^{++} in muscle, which occurs early in ER, is directly related to the degree of muscle destruction and administration of Ca^{++}. Reversal of hypocalcemia may in fact worsen heterotopic calcification and exacerbate hypercalcemia during the resolution phase. Hypocalcemia should only be treated if the patient has evidence of cardiac dysrhythmias or seizures.

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 a cause for concern, especially if persistent and/or greater than 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.

7. Consult Nephrology: Providers can contact nephrology at any time by emailing their Surgeons General's specialty advisor for nephrology. The term "Acute Renal Failure" includes "Acute Kidney Injury (AKI)." The diagnostic criteria for AKI include any one or more of the following: 1) an increase of serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/L) within 48 hours, 2) a serum creatinine ≥1.5 times baseline level within previous 7 days,)urine output of <0.5 ml/kg/hr for 6 to 12 hours).[16] 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.[29] These criteria include both absolute and percentage change in serum creatinine to accommodate variations related to age, gender, and body mass index and reduce the need for a baseline creatinine; the criteria do require at least two creatinine values within 48 hours. Although the urinary output (UOP) criteria were included on the basis of its predictive importance, it is recognized that UOP may not be routinely measured in non-ICU settings. The 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.

Renal replacement therapy is based upon the judgment of the consultant nephrologist. Criteria to consider renal replacement therapy are not based upon serum creatine kinase or myoglobin levels, but by the status of renal impairment, with complications such as life-threatening hyperkalemia, hypercalcemia, hyperazotemia, anuria or hyperhydration without response to diuretic therapy.[16]

8. Hospital Discharge Considerations: Limited guidance is available for transitioning to discharge after CK levels start down-trending and when clinical symptoms have improved. In a series of 30 hospitalized active duty service members for ER, mean CK level for discharge was 23,865 U/L with a wide range (1,410-94,665 U/L).[37] Although most were discharged after CK down-trended, it is only one parameter clinicians should utilize to assess discharge.

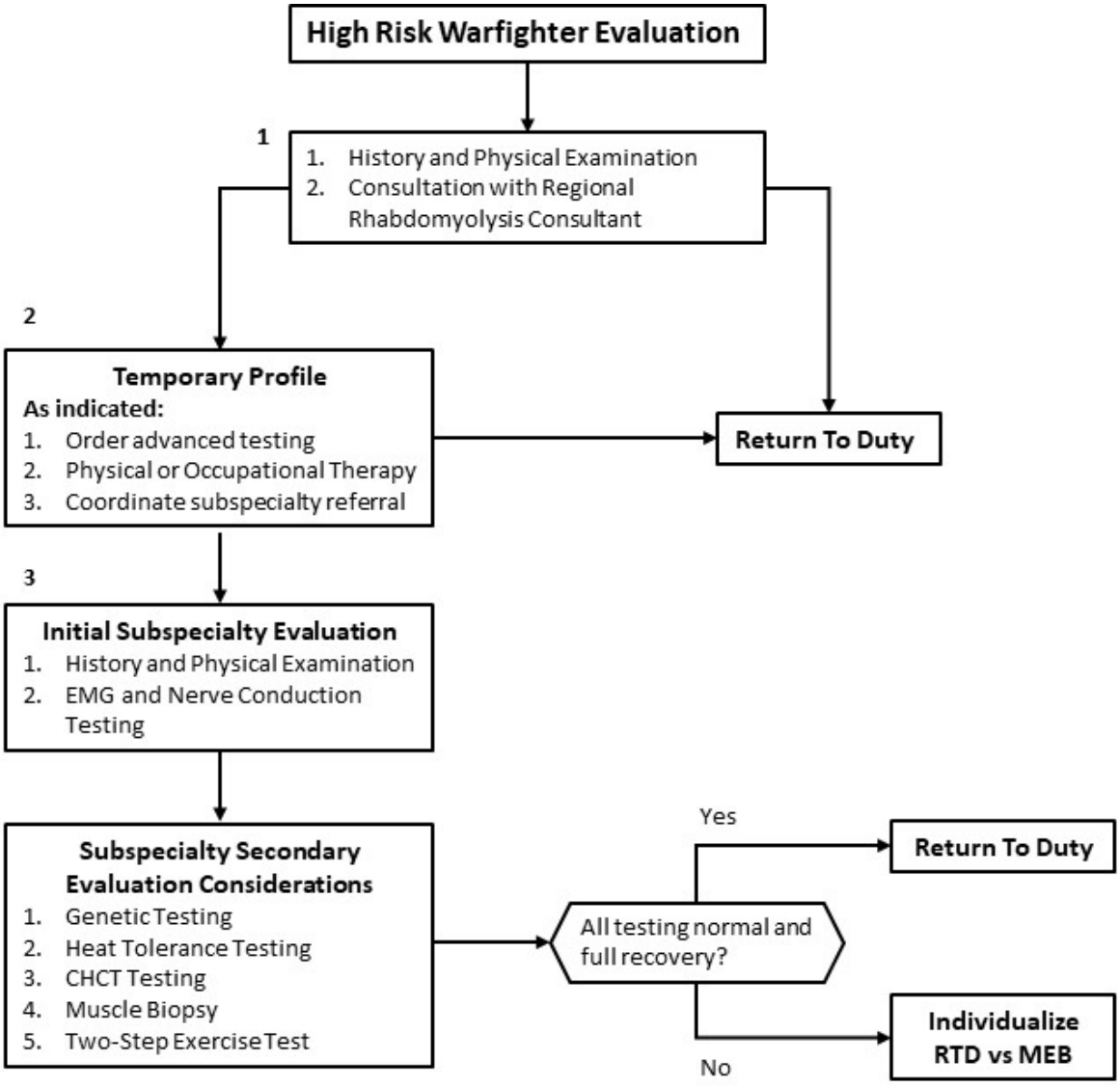
We recommend the following protocol to allow safe discharge from the hospital. After admission and appropriate treatment, discharge may be considered after demonstrating down trending CKs, improving symptoms, improving or improved AKI and metabolic abnormalities, no additional complications, and a reliable plan for continued follow up and profiling. IV fluids may be titrated off at CK of 32,000 U/L*, and a trial of oral hydration may commence. Oral hydration with IV access left in place overnight and continued down trending of CK will ensure that oral hydration can be successfully managed as an outpatient with close follow-up.

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

Upon discharge, consider specialty consultation for duty implications and MEB consideration. After being discharged, the post-discharge follow-up and profiling should address their clinical condition and any comorbidities. ER patients whose serum creatinine values return to baseline may still be at risk for repeated AKI episodes up to approximately 6 weeks after the event, especially in a setting of dehydration or nephrotoxin exposure. 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 nephritis, even if their serum creatinine has returned to "normal". Any ER patient whose renal function has not returned to baseline level after 2 weeks should be referred to nephrology. Providers can contact nephrology at any time by emailing their Surgeons General's specialty advisor for nephrology.

9. Proceed to Annotation 11, Algorithm I.

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



Annotations to Algorithm III

1. Consultation with Regional Rhabdomyolysis Expert: Consultants can be facilitated through contact with the CHAMP Warrior Heat and Exertion Related Event Collaborative (WHEC). https://www.hprc-online.org/resources-partners/whec. Contact WHEC using HPRC's Ask the Expert feature. To make sure you reach the appropriate experts, please include "WHEC" in the subject line of your email.

2. Order Laboratory Tests as Directed by Regional Consultant: Testing may include any of the following serum tests to assist in ruling out metabolic myopathic conditions: [12,38]

- Serum Lactic Acid
- Plasma Amino Acids
- Plasma Carnitine
- Urine Organic Acids
- Plasma Acylcarnitine Profile

3. Subspecialty Evaluation: subspecialty testing will be synchronized and ordered by the tertiary care provider. Testing may include and all of the following tests to assess for underlying myopathic or mitochondrial conditions.[12,39]

Exercise Intolerance Panel: The Exercise Intolerance Mutation Profile (EIMP) is used to help determine whether a patient has mutations/variants in a short list of genes associated with susceptibility to ER:

- EIMP looks for the following:
- Carnitine Palmitoyltransferase II Deficiency
- → CPT2 Gene: S113L, 413delAG, P50H, R503C, G549D, R631C
- Myophosphorylase Deficiency (McArdle's disease)
- → PYGM Gene: R49X, G204S
- Myoadenylate Deaminase Deficiency
- → AMPD1 Gene: Q12X, P48L

Myoglobinuria Test Panel: Myoglobinuria Test Panel (MTP) tests individuals with exercise intolerance-related weakness, pain, cramping, and idiopathic myoglobinuria. MTP detects specific enzymes related to metabolic function for certain diseases. The myoglobinuria test panel should always be performed in conjunction with a standard muscle biopsy to include frozen sections with full histochemistry (available through AFIP).

- MTP tests for the following diseases:
- Phosphofructokinase deficiency (PFK)
- McArdle's disease
- Tarui's disease
- Phosphoglycerate Kinase deficiency (PGK)
- Phosphoglycerate mutase deficiency (PGAM)
- Lactate Dehydrogenase deficiency (LDH)
- Glycogen, Phosphorylase A+ Total deficiency (Ph)
- Phosphorylase B kinase deficiency (PhK)

- Carnitine Palmitoyltransferase 2 deficiency (CPT2)
- Myoadenylate Deaminase deficiency (MAD)

Caffeine-Halothane Contracture Testing (CHCT): Caffeine-Halothane Contracture Testing (CHCT) is performed using a muscle biopsy specimen to detect malignant hyperthermia. Patients who carry the MH gene may also be susceptible to ER. During local anesthesia, approximately 2 grams of muscle are taken from a two- to three-inch incision in the thigh. Six fresh muscle biopsy strips 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 drugs used for general anesthesia. MH, a dominantly inherited disease, causes the body temperature to rise rapidly and induces severe muscle contractions under general anesthesia. Left untreated, the likelihood of organ failure and potential death is high 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, 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 includes a 5-minute step test, 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**.

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 1 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 U/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.

Table 1. High Risk Markers

CK >20,000 U/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)[16,40]
Dark urine or confirmed myoglobinuria
Metabolic abnormality (e.g., hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, acidosis)
Sickle cell trait carrier
Limited patient follow-up (e.g., trainee lives alone)

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