Clinical Practice Guideline for the Management of Exertional Rhabdomyolysis in Warfighters

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Introduction:

1. Exertional rhabdomyolysis (ER) is a common disorder encountered in the military setting. This disorder can be precipitated by a number of factors, but is frequently associated with unaccustomed levels of exertional stress or as a complication of dehydration and/or exertional heat illness, in particular, heat stroke.

2. Although the majority of warfighters who experience ER can be safely returned to duty, some may be at risk for future recurrences. These recurrences may limit the effectiveness of the warfighter and potentially predispose to serious injury, including permanent disability and death.

3. Primary care providers confronted by warfighters with ER face difficult clinical decisions beyond the initial identification and treatment. These decisions include: a) who can be safely returned to duty; b) how should a patient or warfighter be “profiled;” c) how long should the profile period be; and d) does the warfighter warrant further medical evaluation for an underlying disorder, e.g. a metabolic myopathy, and perhaps referral for a medical evaluation board (MEB) in the Army or a physical evaluation board in the Navy.

4. This consensus clinical practice guideline, jointly constructed with the US Military and the Israeli Defense Force is designed to assist providers in assessing and managing challenging ER cases. An algorithm with annotations to assist in the initial management and subsequent recurrence risk stratification process, as well as appropriate profiles, is included.
Algorithm:

1. Warfighter with a Recent History of Exercise, and **Severe Muscle Pain** with or without **Cola Colored Urine**
   - 2. Heat-Associated Injury?
     - Yes 3. Manage as per Army Technical Bulletin 507 and AR 40-501
     - No

4. **Physiologic Muscle Breakdown**

5. Severe muscle pain with:
   1. CK 5X ULN, or
   2. UA positive for blood, with no RBCs
   - Yes 9. Evaluate and Manage per Appendix II Screen for Initial “High Risk” Markers
   - No

6. 1. Limited Duty Profile (Appendix I/Phase 1) Follow-up 24 hr UA and CK
   - No

7. UA positive for blood with no RBC’s or CK 5X ULN
   - Yes

8. 1. Temporary Profile (Appendix I/Begin Phase 2)
   2. Consider acetaminophen
   3. Consider PT referral
   - No

9. 1. Temporary Profile
   2. Appendix I, Begin Phase 1
   3. 24-72 hour reassessment CK, Creatinine, and UA and per Appendix I
   - No

10. Upon Discharge, Assess for Medical Evaluation Board

11. Proceed with MEB

12. Yes

13. No

14. Normal

15. Complete Appendix I Return to Duty Protocol

1. Temporary Profile
2. Clinical Consultation (Phone or Electronic) with Regional Rhabdomyolysis Expert (Appendix III)
3. MEB Consideration

Recurrence Risk Stratification At 2 Weeks from Injury Date
1. **Severe Exercise-Induced Muscle Pain with or without Cola Colored Urine.** Muscle pain usually presents within the first 24-72 hrs after extreme or non-familiar exercise training, in particular when there has been a significant amount of eccentric exercise, e.g. pushups or squats. Delayed onset muscle soreness (DOMS) can be a symptom of ER. DOMS is best described as muscles that become sore and stiff one to three days after a bout of moderate to strenuous exercise. Symptoms and findings that distinguish **severe exercise-induced muscle pain** (possible rhabdomyolysis) from typical physiologic muscle breakdown and/or DOMS include pain out of proportion to what one would normally expect from the activity; muscle swelling; significant limitation of active and passive range of motion; weakness, especially in the hip and shoulder girdle muscles; the presence of cola colored urine; and persistent pain and soreness greater than five days after the precipitating activity. It should be noted that on rare occasion rhabdomyolysis can present with new cola colored urine in the absence of severe muscle pain. This finding in a warfighter should prompt the same initial diagnostic evaluation.

The clinician’s judgment is critical to the determination of severe muscle pain, as in many cases, this determination results in evacuation from the field for a CK determination and further assessment. In the absence of the previously described signs and symptoms (pain out of proportion to what one would normally expect from the activity; muscle swelling; significant limitation of active and passive range of motion; weakness, especially in the hip and shoulder girdle muscles; the presence of cola colored urine; and persistent pain and soreness greater than five days after the precipitating activity) the clinician should develop a careful plan to protect (rest and hydration) and re-evaluate the warfighter. The authors recommend that this evaluation be performed no later than 24 hrs
after the initial assessment. If there is progression of pain, or the presence of aforementioned signs and symptoms, the warfighter should be evacuated.

2. **Heat-Associated Injury.** Heat associated injuries include 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:

   a) **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.

   b) **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.

   c) **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 can be complicated by organ and/or tissue injury, systemic inflammatory activation, and disseminated intravascular coagulation.

3. **Management of Heat-Associated ER.** Management of ER as a complication of exertional heat illness is detailed in the AR 40-501 revision (http://champ.usuhs.mil/chclinicaltools.html) and the military technical bulletin, Heat Stress Control and Heat Casualty Management (TB MED 507/AFPAM 48-152).¹ ²
4. **History, Physical Examination and Diagnostic Testing.** The medical provider should perform a targeted history and physical examination to confirm a diagnosis consistent with either physiologic muscle breakdown (ICD-9 Unspecified Muscle Strain 729.5), or exertional rhabdomyolysis (ICD-9 Rhabdomyolysis 728.88). The provider should specifically inquire about the use of medications, dietary or performance enhancing supplements. If the examination renders a different diagnosis, further evaluation and work-up should be directed appropriately. Otherwise, severe muscle injury should be evaluated at this point with a serum creatine kinase (CK), chemistry profile including BUN and creatinine, and a urinalysis (UA) with microscopic examination.

5. **Diagnosis of ER.** Rhabdomyolysis is defined as the “breakdown of muscle fibers”, which results in muscle fiber contents being released into the systemic circulation. Although rhabdomyolysis has the connotation of being an abnormal condition, in actuality it can be a normal result of strenuous exercise and is countered by repair to facilitate adaptation for future strength gains. However, rhabdomyolysis can be overwhelming and devastating 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, and other incompletely understood contributing factors. The potential devastating consequences of exertional rhabdomyolysis include renal failure, compartment syndrome, and death. In addition, exertional rhabdomyolysis may be the result of an underlying metabolic or myopathic process that predisposes the warfighter to recurrence. Accordingly, this expert panel identifies the important step of not only treating for potential complications, but additionally risk stratifying the individual for risk recurrence.

Athletes and warfighters consistently have higher baseline CK levels as a result of ongoing muscle injury and repair than non-active adults. In addition; gender and ethnic
variation may contribute to unique baseline CK levels. 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.\textsuperscript{3,4} Although the diagnostic criteria for
pathologic ER are somewhat controversial, this guideline suggests a CK level 5X the upper
limit of normal (ULN) or greater, and/or a UA that is positive for blood in the absence of
RBCs (considered an indirect marker for the presence of myoglobin) to enter this
management and treatment algorithm. When possible a serum or urine myoglobin or both,
should be obtained. It is the authors’ expert opinion that this level and definition provide the
greatest safety net in assisting the clinician in the initial management of this often confusing
condition.

6. **Management.** The warfighter is placed on a temporary profile for physiologic muscle
breakdown (muscle strain ICD-9 729.5) (http://champ.usuhs.mil/chclinicaltools.html) and started
on a rehabilitation and return to duty program initially emphasizing strict light indoor duty,
complete rest from physical training, oral hydration, and a mandatory follow-up examination in
24hrs (Appendix I/Phase 1).

7. **Urinalysis and CK.** Patients who were initially diagnosed with physiologic muscle
breakdown (muscle strain), but failed to meet criteria for ER, should be reevaluated by a
knowledgeable clinician within 24 hours. At this time a repeat urinalysis and CK should be
performed. If the patient does not dip positive for the presence of blood, (no RBCs), and the CK
is less than 5X ULN, the warfighter may be gradually returned to duty as determined by the
treating provider using the guidance from Appendix I. Any warfighter who tests positive for
urine blood or demonstrates a CK greater than 5X ULN, should be re-evaluated for ER. (See #9
below).
8. **Temporary Limited Duty Profile.** At the 24 hour follow up, the warfighter diagnosed with physiologic muscle breakdown or DOMS should be continued 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 I. (http://champ.usuhs.mil/chclinicaltools.html). The primary care provider is encouraged to consider referral to physical therapy for rehabilitative supervision as clinically indicated. Additionally, consideration can be given to a short course of acetaminophen for pain relief as needed.

9. **Evaluate and Treat (See Appendix II); Screen for Initial “High Risk” Markers.** The warfighter is diagnosed with Exertional Rhabdomyolysis and should be appropriately screened for High Risk Markers, which include: CK >5,000; potential compartment syndrome; renal insufficiency; metabolic abnormality; urinalysis positive for blood with no RBC’s, and limited patient follow-up.

10. **No High Risk Markers.** The warfighter should be placed on a limited duty profile that excludes field duty, aerobic or anaerobic exercise per Appendix I recommendations (Rhabdomyolysis- Low Risk Profile in the website parallels the Appendix I recommendations) (http://champ.usuhs.mil/chclinicaltools.html). The warfighter should be re-evaluated in 24 hrs. If CK is still elevated and/or the UA is still positive, continue limited duty profile and reevaluate in 24 to 72 hr intervals, as per clinical judgment. When CK value is less than five times the upper limit of the lab’s normal range and the UA has returned to normal, the warfighter begins a graduated return to duty per Appendix I/profile. It is strongly recommended that the return to duty program should be supervised by a physical therapist or occupational therapist.

    When a Warfighter has been admitted for inpatient care, the discharge follow-up and profiling is to correspond to their clinical condition on discharge.
11. **Triage to Medical Treatment Facility.** The warfighter should be referred to a Local Medical Treatment Facility (ER) for IV therapy, further laboratory evaluation, and assessed for admission, if these cannot be done at the local Troop Medical Facility (Appendix II). Additional laboratories should include but are not limited to: urine myoglobin, serum calcium, BUN, CR, phosphate, uric acid, PT/PTT/INR, ECG. Further management considerations are detailed in Appendix II.

12. **Upon discharge, Assess for MEB Consideration.** MEB disposition for Warfighters with Exertional Rhabdomyolysis:

   a. Individual episodes of exertional rhabdomyolysis are not cause for an immediate MEB referral. However, warfighters who experience recurrent exertional rhabdomyolysis or a single episode with either severe systemic complications (e.g. compartment syndrome), or of such a nature that sequelae interfere with successful performance of duty, require referral to an MEB.

   b. Warfighters demonstrating any of the following criteria should be referred to an appropriate specialist for consideration of MEB:

      1) Persistent residual kidney injury (> two weeks out);

      2) Persistent elevation of CK above five times the upper limit of the lab normal range or delayed clinical recovery despite rest of at least two weeks;

      3) History of sickle cell trait.

If MEB is not warranted and the warfighter is less than 2 weeks from injury they should be profiled and followed per Appendix I. At 2 weeks from injury the warfighter will be risk stratified for recurrence. If MEB is warranted, the warfighter should be given a permanent profile (Rhabdomyolysis- High Risk Profile) ([http://champ.usuhs.mil/chclinicaltools.html](http://champ.usuhs.mil/chclinicaltools.html)) and referred
appropriately. These Warfighters should be followed in 72 hours and as needed thereafter, based on their clinical condition.

13. **Recurrence Risk Stratification at 2 weeks from Date of Injury.** In order to define the case as “high risk” for recurrence at least one of the following conditions must exist or be present:

   a. Delayed clinical recovery (more than a week) when activity has been restricted;

   b. Persistent elevation of CK above five times the upper limit of the lab normal range despite rest of at least 2 weeks;

   c. Rhabdomyolysis complicated by acute kidney injury (AKI) that does not return to baseline within two weeks;

   d. Rhabdomyolysis after low to moderate workload;

   e. Personal or family history of rhabdomyolysis;

   f. Personal or family history of recurrent muscle cramps or severe muscle pain that interferes with activities of daily living or military performance;

   g. Personal or family history of malignant hyperthermia; or family history of unexplained complications or death following general anesthesia.

   h. Personal or family history (if personal status unknown) of sickle cell disease or trait;

   i. Complicated by drug or supplement use (e.g. statin, ephedra, steroids, creatine) or any other over-the-counter “performance enhancing” or weight loss products. While supplements do not imply a medical condition that would necessarily warrant an MEB or detailed work-up, individual as well as unit education may be warranted;

   j. Personal history of significant heat injury; or
k. CK peak > 100,000 U/L.

In order to define the case as “low risk” for recurrence none of the high risk conditions should exist, and at least one of the following conditions must exist or be present:

1) Clinical (one week) and laboratory (two weeks) recovery with exercise restriction;

2) Highly physically trained warfighter with a history of very intense training;

3) No personal and family history of rhabdomyolysis or previous reporting of exercise-induced severe muscle pain, muscle cramps, or heat injury;

4) Existence of other rhabdomyolysis cases in the same training unit;

5) Concomitant viral illness or other infectious disease.

14. **High Risk.** These warfighters should be referred to or discussed with an appropriate specialist or regional consultant for further management and to consider evaluation for an underlying disorder that may predispose to recurrent injury (http://champ.usuhs.mil/). The evaluation may include, but is not limited to: muscle biopsy, EMG, caffeine-halothane muscle contracture test, and/or rhabdomyolysis exercise challenge test (See Appendix III). Return to duty and profiling is individualized.

15. **Low risk.** Continue progressing through Appendix I return to duty protocol, as determined by the treating medical provider with the corresponding profile, as stated above.
References


Appendix I

Physiologic muscle breakdown and
Low Risk Warfighter with Exertional Rhabdomyolysis:
Return to Duty Guidelines

1) Phase 1:

- Strict light indoor duty for 72 hrs; encourage oral hydration, salting of food.
- No weight training
- Must sleep eight consecutive hours nightly.
- Must remain in thermally controlled environment.
- Must follow-up in 24 hrs for repeat CK/UA.
- If at the 24 hours follow up the CK value continues to be less than five times the upper limit of the lab normal range and the UA continues to be normal, may begin Phase 2 after the initial 72 hours of limited duty. (Physiologic Muscle Breakdown Profile)
- If at the initial 24 hours follow up the CK is more than five times the upper limit of the lab normal range and/or the UA is positive for blood with no RBC’s the Soldier needs to have been cleared per Appendix II for outpatient management. The Warfighter is to continue on Phase 1 delineated above (Low Risk Rhabdomyolysis Profile) and followed in 24 hours with CK, creatinine and UA. After this, or upon hospital discharge, the Warfighter will be followed every 24-72 hours as per clinical judgment.
- When CK value is less than five times the upper limit of the lab normal range and the UA has returned to normal, begin Phase 2. Otherwise remain in Phase 1 and return every 72 hrs for repeat CK/UA until the criteria stated above are met.
- If CK remains greater than five times the lab upper limit of normal and/or the UA is persistently abnormal for two 2 weeks, refer for expert consultation.

2) Phase 2:

- Begin light outdoor duty, no strenuous physical activities.
- Light weight training.
- Supervised physical activity at own pace and distance.
- Follow-up with care provider in one week.
- If no return of clinical symptoms, 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 myalgias persist without objective findings beyond 4 weeks, consider specialty evaluation to include psychiatry.

3) Phase 3:

- Return to regular outdoor duty and physical training.
- Follow-up with care provider as needed.
Algorithm for Treatment of Acute Exertional Rhabdomyolysis

Warfighter Presents with:
Severe muscle pain with:
- CK 5X NL, or
- UA positive for blood, with no RBCs

“High Risk” Markers?
1. CK >5,000
2. UA positive for blood, with no RBCs
3. Potential Compartment Syndrome
4. Renal Insufficiency
5. Metabolic Abnormality
6. Limited Patient Follow-Up

Presence of “High Risk” Markers?
- No
- Limited indoor duty for remainder of day
  - Medical re-evaluation on following day; oral re-hydration

Refer to Local Medical Treatment Facility
- Labs should include but are not limited to: urine myoglobin, serum calcium, BUN, CR, phosphate, uric acid, PT/PTT/INR, ECG. Note: elevations in ALT and AST probably reflect muscle release – GGTP may be necessary to assist in identification of liver injury.
- IV rehydration is recommended with hospital admission individualized based upon: metabolic and renal status; hydration status; patient follow-up. ICU admission warrants intensivist consultation.

Admission Management Considerations
- IV hydration with NS (1-2L/hr) to maintain urine output >200cc/hr, until CK levels begin to decrease; consider intravascular volume monitoring if patient does not respond to initial therapy.
- Foley catheter if anuric or unable to cooperate with Is/Os.
- Observe closely for and manage Compartment Syndrome as Appropriate.
- ABG if lactic acidosis suspected

Positive Urine Myoglobin or Metabolic Acidosis
- Consider Urine Alkalization
  - Alkalize urine if serum lactate >4 or serum or urine pH < 7.2; Goal of urine pH>6.5.

Hyperkalemia
- Consider:
  - D50; Insulin
  - Inhaled B-agonist
  - Calcium/Kayexalate

Phos > 7mg/dl
Or
SYMPTOMATIC hypocalcemia
Or
Acute Renal Failure
Or
Refractory hyperkalemia
- Consult Nephrologist
  - For Possible Dialysis
1. **Diagnosis.** A diagnosis of rhabdomyolysis is made when there is clinical evidence of myonecrosis with release into the systemic circulation of muscle cell contents, including myoglobin, creatinine, CK, organic acids, potassium, aldolase, lactate dehydrogenase, and 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 there is clinical evidence of rhabdomyolysis, such as muscle pain and weakness, then CK levels in excess of five times normal are accepted as evidence of significant muscle breakdown and are generally considered to be consistent with a diagnosis of rhabdomyolysis. The provider is reminded that there are many additional causes of CK elevations, such as inflammatory myopathies and muscular dystrophies; these patients are not considered to have rhabdomyolysis.

Myoglobin is theoretically the best marker and a diagnostic cornerstone because myoglobinuria does not occur in the absence of rhabdomyolysis. However, testing for serum or urine myoglobin is problematic and not always consistent. Myoglobin is normally bound to plasma globulins, and therefore only a small fraction reaches the glomeruli. 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 eventually the renal tubules. Elevations in serum myoglobin occur before a rise in serum CK, but the elimination kinetics of serum myoglobin is more rapid than that of CK, which makes the often evanescent rises 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, one can assume, in the appropriate clinical setting, that the positive dipstick reading reflects the presence of myoglobin. In addition, for field expedient analysis, the supernatant (top portion) of spun urine sediment will be brown in myoglobinuria and pink in hemoglobinuria.

2. **High Risk Markers.** After diagnosing a warfighter with exertional rhabdomyolysis, the clinician must carefully screen for initial clinical "high risk" markers which have been demonstrated to place the patient at increased risk for complications. High risk markers include:

   a. CK >5,000
   b. UA positive for blood, with no RBCs
   c. Potential Compartment Syndrome
   d. Renal Insufficiency
   e. Metabolic Abnormality
   f. Limited Patient Follow-Up

The presence of any of the above "high risk" markers warrants triage of the patient to a provider and/or setting familiar with the diagnosis and management of exertional rhabdomyolysis. A UA positive for blood, with no RBCs, as well as renal insufficiency of any degree, qualify as high risk markers in this setting. Common metabolic abnormalities that should be considered "high risk" include, but are not limited to, hyper- and hypokalemia, acidosis and hyponatremia. These abnormalities do not in and of themselves warrant admission, but access to a level of care with further diagnostic and treatment capabilities. These "high risk" markers are a guide, and do not supercede clinical judgment.
Currently, no clinical prediction rule exists for risk-stratifying patients with rhabdomyolysis or for determining in whom acute renal failure will develop. However, CK levels greater than 5,000 U/L are thought to portend an increased risk for acute renal failure. Patients with mild symptoms and serum CK levels less than 5000 U/L are considered to be at lower risk and may be treated as outpatients with oral rehydration, limited physical activity, and careful follow-up. In patients with CK levels over 5,000 U/L, or a urinalysis positive for blood without RBC’s, hydration is best accomplished by aggressive intravenous fluid therapy and observation, either in an outpatient or inpatient setting, and accordingly the patient should be in or moved forward to a facility with these capabilities.

3. Refer to Local MTF. The setting should have the capability for additional laboratory evaluation, short term observation as well as access to intravenous therapy. Further lab work should be obtained to include: urine myoglobin, serum calcium, BUN, CR, phosphate, uric acid, PT/PTT/IN, and liver function tests if not already obtained. In addition, an ECG should be obtained, which can assist in the assessment and management of hyperkalemia. Intravenous therapy should be initiated on "high risk" individuals. Initial therapy should begin with isotonic fluids, and adjusted as determined by the treating clinician. After 2 to 3 liters of fluid has been administered, and the treating provider has had an opportunity to assess the patient’s clinical status, laboratories, and capability for follow-up, the decision can be made to discharge for follow-up, or admit for further therapy.

Each and every case needs to be individualized when a decision is made to consider hospital admission. It is the authors’ opinion that warfighters with exertional
rhabdomyolysis with the following complicating factors be strongly considered for hospital admission, regardless of the CK value:

a. exertional rhabdomyolysis and an abnormal metabolic panel;

b. cases where rhabdomyolysis has been complicated by exertional heat injury; or

c. patients with limited or unreliable follow-up care.

d. exertional rhabdomyolysis with sickle cell

In the absence of complicating factors the clinician should consider admission for CK levels $>10,000$. Please note that a urinalysis positive for blood and with no RBC’s does not necessitate admission on its own but needs to be followed to resolution; BUN and creatinine need to be appropriately followed.

4. Admission Management Considerations. In patients with CK levels over 5,000 U/L, hydration is accomplished by aggressive intravenous fluid therapy with isotonic fluids at a rate that will result in a urine output of 200 mL/hr until CK levels begin to decrease. If the patient does not respond to initial intravenous fluid therapy, clinical consultation should be obtained with the appropriate specialist. In addition, when fluid resuscitation fails to correct intractable hyperkalemia and acidosis, dialysis should be considered.

Treatment of the warfighter with rhabdomyolysis is focused on preventing complications, and is guided by continually assessing vital signs, serial physical examinations, laboratories, and urine output. Peak CK levels are generally reached within 2 to 3 days. Although there are no validated hydration algorithms, intravenous hydration is generally not discontinued until CK levels are decreasing, and there is good urine output. A Foley catheter may be required to follow urine output, as well as more aggressive techniques to assess volume status, as determined by the treating clinician. A graded approach from non-invasive intravascular volume monitoring to minimally invasive
systolic hydration, accomplished by aggressive intravenous fluid therapy with isotonic fluids volume variation/pulse pressure variation, or more invasive techniques such as central venous or pulmonary artery occlusion pressures, should be entertained. Minimally invasive and invasive techniques should be performed under the direction of an intensivist in a critical care unit.

The use of furosemide in this setting is discouraged in the absence of symptomatic volume overload; specifically 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.

Compartment syndrome is a well-described late complication, as well as a potential cause, of rhabdomyolysis. In the proper clinical setting the following signs and symptoms should raise suspicion of a diagnosis of compartment syndrome: disproportionate pain relative to the injury; pain on passive stretching of a muscle; or paresthesias of the involved extremity. Clinical suspicion should be followed by urgent consultation with a surgeon or orthopedic specialist to expeditiously measure compartment pressures. Tissue pressures in excess of 30 mm Hg should prompt consideration for surgical fasciotomy.

5. **Urine Alkalization.** There are no large, randomized trials to suggest any clinical advantage to alkalization over aggressive hydration for patients with exertional rhabdomyolysis; however, this procedure is not infrequently performed. The clinician needs to be cautious as alkalization can potentially worsen hypocalcemia. If the decision is made to alkalize the urine, the goal urine pH is > 6.5. 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. Consider consultation if urine pH does not rise or serum Ca++ drops.

6. **Hypocalcemia.** Deposition of Ca++ in muscle, which occurs early in rhabdomyolysis, is directly related to the degree of muscle destruction and administration of Ca++. Reversal of hypocalcemia may in fact worsen ectopic calcification and exacerbate hypercalcemia during the resolution phase. Accordingly, hypocalcemia should be treated only when clinical symptoms, signs of tetany, or severe hyperkalemia develop.

7. **Consult Nephrology.**

   a. **Definition of Acute Renal Failure:** The term "Acute Renal Failure" has recently been updated to "Acute Kidney Injury (AKI)." Definition and diagnostic criteria for AKI: an abrupt (within 48 h) reduction in kidney function, currently defined as an absolute increase in serum creatinine of either >=0.3 mg/dl (>=25 micromol/L) or a percentage increase of >=50%; or a reduction in urine output (documented oliguria of <0.5 ml/kg per h for >6 h). The criteria include both absolute and percentage change in creatinine to accommodate variations related to age, gender, and body mass index and to reduce the need for a baseline creatinine but does require at least two creatinine values within 48 h. The urinary output (UOP) criteria were included on the basis of the predictive importance of this measure. But it is recognized that UOP may not be measured routinely in non-ICU settings. The diagnosis of AKI on UOP criteria alone requires exclusion of urinary tract obstruction or other reversible causes of reduced UOP. These criteria should be used in context of the clinical presentation and after adequate fluid resuscitation when applicable.

   b. **Risks Associated with Rhabdomyolysis and AKI:** Patients whose serum creatinine returns to baseline still may be at risk of repeated AKI episodes for approximately 6 weeks, 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 rhabdomyolysis should receive fluid (NS or bicarbonate) and acetylcysteine prophylaxis for prevention of contrast-induced nephritis, even if their serum creatinine appears to be "normal".

c. **Referral to Nephrology:** Any rhabdomyolysis patient whose serum creatinine has not returned to baseline level after 2 weeks should be referred to nephrology. Providers are welcome to contact nephrology at any time at nephrology.consult@us.army.mil.
Appendix III

Diagnostic Evaluation of the High Risk Warfighter with a History of Rhabdomyolysis

High Risk Warfighter Evaluation

1. History and Physical Examination
2. Consultation with Regional Rhabdomyolysis Expert

Referral Warranted

1. Temporary Profile
2. Order Exercise Intolerance Panel, Guthrie Laboratory
3. Coordinate Referral

Reassurance

Return to Duty:
Physical or Occupational Therapy Referral

Initial Subspecialty Evaluation:
History and Physical Examination
EMG, Two-Step Exercise Test

Secondary Subspecialty Evaluation:
Consider:
Heat Tolerance Testing
Caffeine-Halothane Contracture Test
Muscle Biopsy to include
Myoglobinuria Panel at Athena Labs
1. **Regional Rhabdomyolysis Expert:** Consultant can be identified at Consortium for Health and Military Performance (CHAMP) website: [www.CHAMP.usuhs.mil](http://www.CHAMP.usuhs.mil).

2. **Exercise Intolerance Mutation Profile:** The Exercise Intolerance Mutation Profile (EIMP) is used to help determine whether a patient has the particular genes that indicate susceptibility to rhabdomyolysis.

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

   Standard collection for EIMP includes 10 cc of blood in EDTA (purple) tubes. Samples can be stored in the refrigerator up to 24 hours before shipment. For shipment, tubes are sent at room temperature. It is recommended that samples are shipped Monday – Wednesday.

   Forms for shipment to Guthrie labs: [http://www.rgbgl.org/forms/mutationpro.htm](http://www.rgbgl.org/forms/mutationpro.htm)

   Contact: Clinical Laboratory – Genetics
            The Buffalo General Hospital
            Room A-762, 100 High St NY 14203
            (716) 859-7741 FAX (716) 859-7749
            Georgirene D. Vladutiu, Ph.D., Director
            Website: [http://www.rgbgl.org](http://www.rgbgl.org)

3. **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)

   Standard collection for MTP requires 250 mg of muscle. The muscle must be flash frozen in liquid nitrogen and stored in Cryoval tubes. For shipment, 10 lbs of dry ice must be included. It is recommended that samples are shipped Monday – Wednesday. Cryoval tubes and shipping boxes are provided by Athena Diagnostics, Inc if requested.

   Call Athena Diagnostics for shipment forms.

   Contact: Athena Diagnostics, Inc.
            Four Biotech Park
            377 Plantation Street
            Worcester, MA 01605
            (716) 859-7741 Fax: 508-753-5601
            Website: [www.athenadiagnostics.com](http://www.athenadiagnostics.com)
4. Caffeine-Halothane Contracture Testing (CHCT): Caffeine-Halothane Contracture Testing (CHCT) is a muscle biopsy test performed under local anesthesia used to detect malignant hyperthermia. Patients who carry the MH gene are also susceptible to rhabdomyolysis. During anesthesia, approximately 2 grams of muscle is taken from a two- to three-inch incision in the thigh. Six fresh muscle biopsy strips are soaked in either caffeine or halothane solutions and are observed for contractions. The sensitivity is 97% and the specificity is 78% for CHCT.

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 rhabdomyolysis evaluation performed by a physician is recommended. A rhabdomyolysis 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 schedule a test, contact Dr. Muldoon (301-295-3532) or Dr. Capacchione (301-295-3141) at USUHS.

5. Rhabdomyolysis Two-Step Challenge Test:

The step test includes stepping up and down two stairs (30 cm height each) for 5 minutes at a pace of 54 steps/min (using a metronome) followed by 15 knee bends completed within 1 minute (3 seconds count down and two seconds count up). A backpack weighted at 30% of body weight is worn during both tests. A blood sample will be taken before, immediately after completing the exercise, 48 and 72 hours after completing the test. The participant will be defined as high responder when the change of CK level from baseline will be greater than 230 U/L. The participant should avoid exercise for at least 48 hours before the test.