**Defense Health Agency**
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**Military-Specific Care Clinical Community & Environmental Medicine Working Group**

***DHA Practice Recommendation:***
*Inpatient Management of Exertional Rhabdomyolysis*
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# Falls Church, Virginia

**Inpatient Management of Exertional Rhabdomyolysis**

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# Inpatient Management of Exertional Rhabdomyolysis, Version 1.0

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## Purpose

This PR is intended to provide a synopsis of care recommended to assist providers in the assessment and inpatient management of Exertional Rhabdomyolysis (ER). The guidance in this document is applicable to Service members as well as beneficiaries or others who may suffer from ER. Separate PRs are available for the initial management of ER and for the management of a patient with recurrent or high-risk ER. This PR is based on Clinical Practice Guidelines (CPG) constructed jointly between the U.S. Military and the Uniformed Services University of the Health Sciences, which were originally published in November 2017 and revised in May 2020. The original CPG can be found here on the Warrior Heat- and Exertion-Related Event Collaborative website located at https://www.hprc-online.org/resources-partners/whec. The use of the name or mark of any specific manufacturer, commercial product, commodity, or service in this publication does not imply endorsement by the Department of Defense.

Specific warfighter management questions can be directed to an Ask-the-Expert function at: https://www.hprc-online.org/ask-the-expert.

## Diagnosis

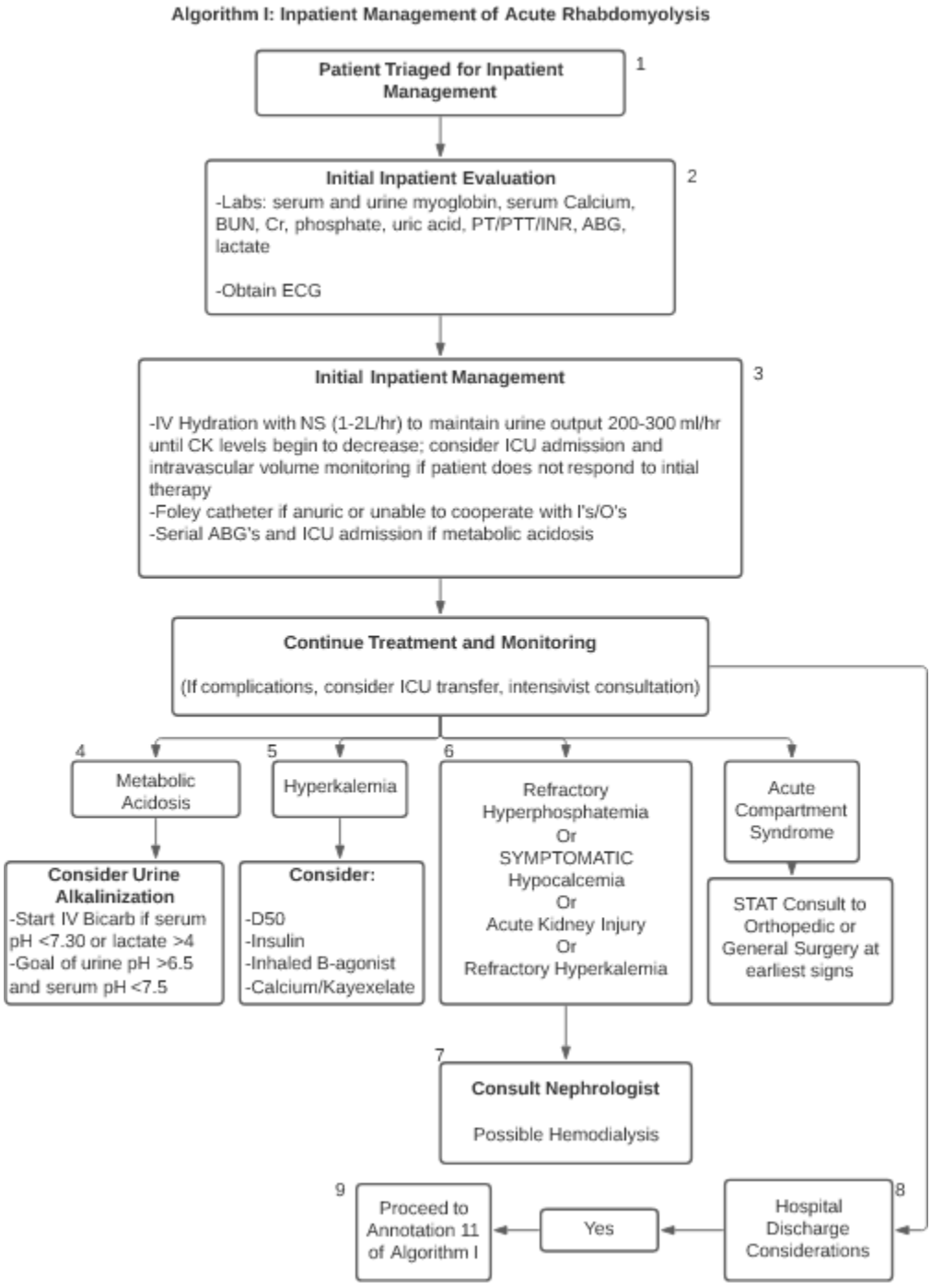
*Introduction and Definition*

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 recently accustomed.[1] It is defined as severe muscle symptoms (pain, stiffness, and/or weakness) AND laboratory evidence of myonecrosis (creatine kinase (CK) level $\geq$ 5X the upper limit of normal) in the setting of recent exercise. 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.

ER remains a serious and prevalent illness among warfighters. In 2018, there were 545 incident diagnoses of rhabdomyolysis likely associated with physical exertion or heatstress.[1] During the surveillance period of a recent study (2014-2018), the rates of incident diagnoses of ER increased from 30 per 100,000 person-years (p-yrs) in 2014 to 40.8 per 100,000 p-yrs in 2016. This decreased slightly in 2017 to 39 per 100,000 p-yrs before increasing again in 2018 to 42 per 100,000 p-yrs.[1]

Although the majority of warfighters who experience ER recover and will be safely returned to duty, some may experience sequelae, while others may be at increased 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.

## Clinical Management



*Annotations to Algorithm 1*[13]
**Abbreviations Legend: Blood Urea Nitrogen (BUN); Creatinine (Cr); Prothrombin Time (PT); Partial Thromboplastin Time (PTT); International Normalized Ratio; Arterial Blood Gas; Electrocardiogram (ECG); Normal Saline (NS); Creatine Kinase (CK); Intensive Care Unit (ICU); Inputs/Outputs (I's/O's); 50% Dextrose Infusion (D50)*

**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, blood urine nitrogen (BUN), creatinine, phosphate, uric acid, prothrombin time (PT) / partial thromboplastin time (PTT) / international normalized ratio (INR), and lateral flow test (LFTs), if not already obtained. Of note, elevated LFTs in the setting of ER are expected, and generally result from myocyte release rather than hepatocellular damage. In addition, an electrocardiogram (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 Intensive Care Unit (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)[2] 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 alkalinization.

Fluid volumes can range from 400 mL/hr, 20 mL/kg in the first 24 hours, to 4 to 8 L per day[2], but at a rate resulting in a urine output of 200-300 mL/hr[3] until CK levels begin to decrease. Large volumes of NS can contribute to hypernatremia and hyperchloremia and, therefore, after initial management we recommend switching fluids to 0.45 NS. If the patient does not respond to initial IV fluid therapy, a clinical consultation with a nephrologist, or other 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 two to three 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 aggressive hydration, so 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 may be controlled with acetaminophen (in the absence of significant LFT elevation). Due to higher risk concerns for inpatient cases nonsteroidal anti-inflammatory drug (NSAIDs) should be avoided. Very limited use of opiates may be additionally considered. CK levels should be drawn periodically every 6-12 hours.

Acute compartment syndrome (ACS) is a well-described potential late complication[2,4] 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 consulting general or orthopedic surgeon.

**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 acute kidney injury (AKI) (OR = 0.175).[5] 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.[5,6] This can be accomplished by administering 2 ampules of sodium bicarbonate diluted in one liter of dextrose 5% in water (D5W) at a rate of 75-125 ml/hr. Monitor serum

potassium (K+), calcium (Ca++) and urine pH every 4 hours. Consider nephrology consultation if urine pH does not rise or if 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 cardiac monitoring should be considered in the event of ECG changes or if 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 any 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 should consider consulting their nearest local or regional nephrologist for assistance. If unavailable then providers can contact nephrology by emailing a Surgeon General's specialty consultant for nephrology. The term "Acute Renal Failure" includes "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, 3) urine output of <0.5 ml/kg/hr for 6 to 12 hours.[7] 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.[8] 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.[7]

**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).[9] 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 limited duty 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 military Medical Treatment Facility (MTF), CK levels were diluted 2x and exact levels over 32,000 were not reported unless specifically requested. Therefore, this protocol uses 32,000 as a cut off criterion 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 medical evaluation board consideration for repeat occurrences.

**Table 1. High-risk Markers**

| |
|---|
| ▪ CK >20,000 U/L |
| ▪ Suspicion for potential compartment syndrome |
| ▪ Acute kidney injury (See Kidney Disease Improving Global Outcomes (KDIGO) criteria, available at https://kdigo.org/guidelines/) |
| ▪ Dark urine or confirmed myoglobinuria |
| ▪ Metabolic abnormality (e.g., hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, acidosis) |
| ▪ Sickle cell trait carrier |
| ▪ Limited patient follow-up (e.g., individual lives alone) |

*Prevention*

The best way to prevent a presentation warranting inpatient admission is prevention of ER at a basic level. Multiple preventive measures exist for reducing the risk of developing ER. The first measure is to develop a basic understanding of proper exercise warm-up, as this has been shown to reduce the risk of musculoskeletal injury.[10] Additionally, increasing exercise levels over time can be protective as opposed to sudden exposure to specific exercises such as high intensity, longer duration, and weight-bearing exercise (eccentric contraction and downhill running).[11] Next, individuals with communicable disease or viral diseases including diarrhea or vomiting should reduce, modify or avoid physical activity to prevent

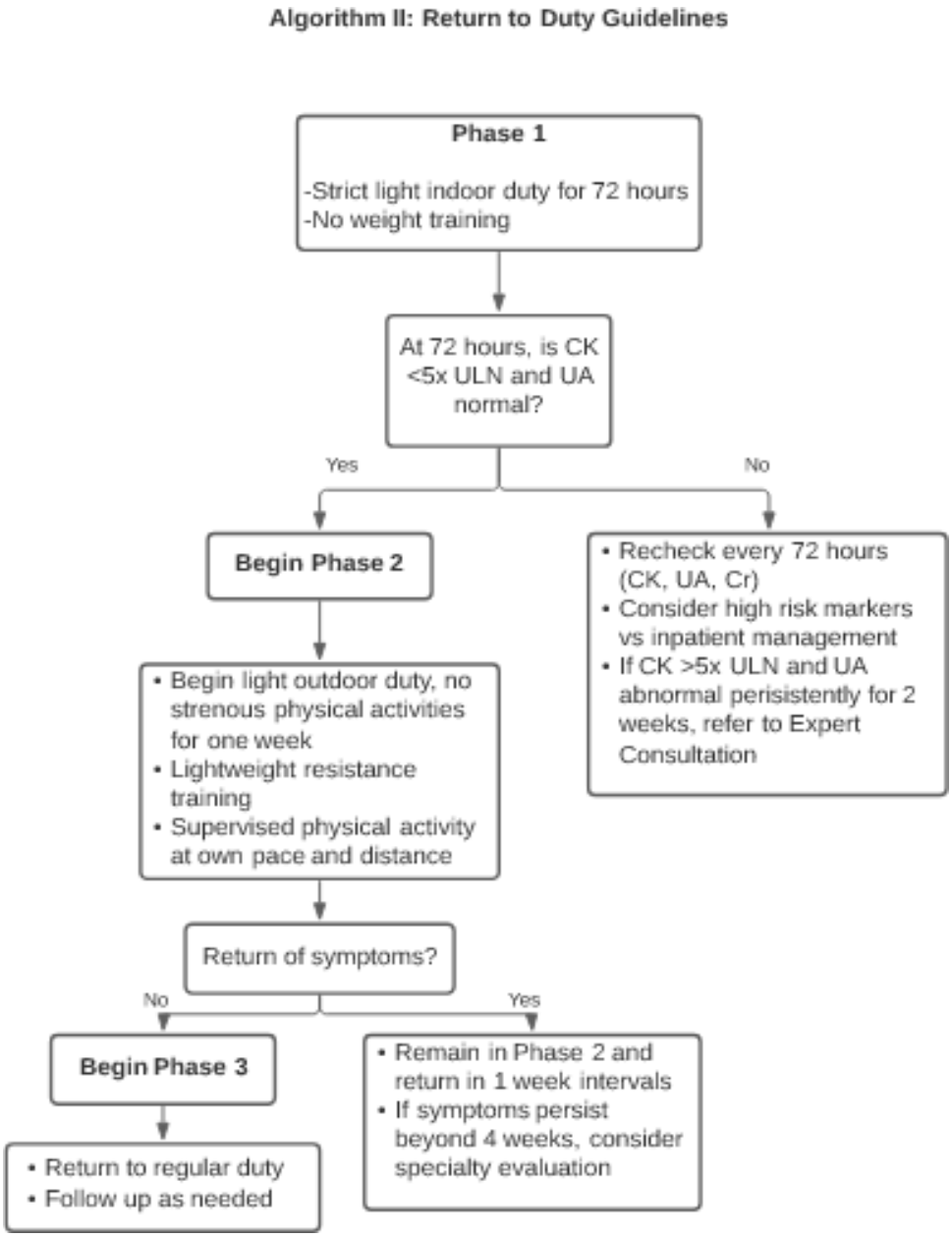
possible development of ER.[12] Environmental factors should also be considered. Taking precautions to avoid exertional heat illness can subsequently reduce the risk of developing ER. Modifying gear or uniform to aid in heat dissipation and providing a cooling mechanism should be considered in settings of high heat or humidity.

*Return to Duty Guidelines*

After being discharged, the post-discharge follow-up and limited duty 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.

In regards to profiling, the warfighter should be placed on a limited duty profile that excludes strenuous field duty activities (e.g., extended marching, obstacle courses, and land navigation). It must also limit aerobic and anaerobic exercise per Appendix recommendations (Rhabdomyolysis- Low Risk Profile in the website, https://champ.usuhs.edu/sites/default/files/2020-11/hprc_whec_clinical_practice_guideline_for_managing_er.pdf, parallels the Appendix recommendations). 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. If the warfighter is on special duty status (e.g., flight, dive, special operations), consultation with specialist in this area is recommended before returning to full duty.

*Appendix. Return to Duty Guidelines for Physiologic Muscle Breakdown and Low Risk Warfighters with Exertional Rhabdomyolysis*




**Phase 1 Annotations:**

- Strict light duty for 72 hours (recommend indoor duty if at all possible) and encourage oral hydration, salting of food to taste;
- No weight training;
- Must sleep seven to eight consecutive hours nightly;
- Must remain in thermally controlled environment.

**Phase 2 Annotations:**

- Advancing light duty, no strenuous physical activities, lightweight resistance training;
- Follow-up with care provider in one week;
- Progression to Phase 3 occurs when there is no significant muscle weakness, swelling, pain or soreness with supervised Phase 2 exercise. If myalgia persists without objective findings beyond 4 weeks, consider specialty evaluation to include psychiatry.

**Phase 3 Annotations:**

- Return to regular duty and physical training;
- Follow-up with care provider as needed.

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## Potential Conflicts of Interest

The Authors declare no conflicts of interest.

## External Peer-Review

N/A

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6 September 2022

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