PEDIATRIC GUIDELINE – RHABDOMYOLYSIS

Brendan Crawford MD, Richard Blaszak MD, Michael Israel MD

Key Points

- Rhabdomyolysis results from numerous causes and ranges in severity with potential for electrolyte abnormalities and/or acute kidney injury (AKI)
- No consensus evidence-based guidelines exist for definition, thresholds for admission, or specifics on type/duration of medical management
- Early aggressive hydration remains primary treatment to prevent serious complications
- For exertional rhabdomyolysis, return to play should occur in graded fashion once clinical symptoms resolve and CK normalized
- Recurrent episodes should prompt evaluation for underlying condition

Preface: These guidelines have been developed for educational purposes and is not intended to be a substitute for individualized professional medical judgment, advice, diagnosis, or treatment.

Definition, Assessment

- Rhabdomyolysis refers to skeletal muscle breakdown leading to release of intracellular contents, such as creatine kinase (CK) and myoglobin, into the bloodstream.
    - Myonecrosis can cause hyperkalemia, hyperphosphatemia, and hypocalcemia
    - Released myoglobin can cause renal tubular injury (pigment nephropathy)
- Numerous mechanisms can cause rhabdomyolysis: direct injury (crush injury, prolonged immobilization), excess exertion (exercise, seizures), infections (viruses, sepsis), prescription drugs (statins, neuroleptics), illicit drugs, toxins (snakebite, brown recluse spider), metabolic myopathies (glycogenosis, lipid metabolism defects), muscular dystrophies, and electrolyte abnormalities
- Viral infections appear to be a more common cause in younger children (Mannix)
    - Viral etiology still associated with AKI (Gardner)
- Exertional rhabdomyolysis (ER) has been associated with a “too much, too fast, too soon” approach whereby the individual is not accustomed to the exercise (Tzietze)
    - NCAA (National Collegiate Athletic Association) has identified numerous factors contributing to outbreaks of ER in athletes
        - Attempt to rapidly “condition” athlete/ deviation from a progressive, periodized improvement plan
        - Exercise focus on single muscle group to failure (high repetitions/load)
        - Intense workouts for punishment/ underperformance
        - Performing eccentric exercises (whereby muscle contracting while lengthened) to fatigue, such as pushups, pullups
        - Novel/ intense exercise following transition period (football player completing vigorous preseason workouts after summer break)
- Numerous other factors contribute to ER including extreme heat, altitude, dehydration, drugs, and athlete medical history
    - Sickle cell trait (SCT) has been associated with ER, but not higher risk of death (Naik, Nelson). Athletes with SCT should not be excluded from participation since precautions can mitigate risk.
    - Athletes with SCT should be encouraged to discuss status with coach/ organization to ensure proper monitoring and decrease likelihood of exercise- related illness. Methods to decrease risk include avoiding dehydration, monitor risk factors (hot/ humid environment, altitude, asthma management), receiving adequate rest, and participation in a extended acclimation program. In individuals with history of ER,

high- risk environments (altitude/heat) may necessitate need for extra precautions/ modification of activity.
- Chronic kidney disease (CKD) is not a common sequela of severe cases (Gelbart)

Diagnosis
- Symptoms include the classic triad of (1) muscle weakness, (2) muscle pain and/ or (3) discolored urine
    - Not all symptoms may be present, as discolored urine can occur in only 5% (Mannix)
    - Oliguria or anuria may be present, and should be queried
- Severe swelling of an extremity should raise concern for compartment syndrome – a surgical emergency!
- Elevations in CK represent primary biomarker for diagnosis, and levels exceeding 5x upper limit of normal (ULN), or greater than 1000 U/L, is common definition, although heterogeneity exists in literature regarding the threshold level
    - Threshold of 5x ULN has high sensitivity but low specificity, as there can be wide spectrum of values in exercising athletes; symptoms and clinical condition remain important to guide management (Lippi)
- Rapid half-life of plasma myoglobin can lead to false- negative testing, and levels are not routinely used clinically for diagnosis
- Normal urine does not have myoglobin, so positive urine myoglobin can be diagnostic
    - Turn-around time of urine myoglobin test may limit initial clinical utility
    - The orthotoluidine ("blood") strip on a urinalysis turns blue in the presence of hemoglobin or myoglobin. Positive "blood" urine dipstick but absence of red blood cells on microscopy rules out hematuria from glomerular, non- glomerular or urologic cause, and supports diagnosis of either myoglobinuria or hemoglobinuria.
- Validated clinical instrument for predicting AKI and mortality has been developed for adults, but no similar pediatric score available (McMahon)

Management
- Identify history of muscle pain (including more severe/ sustained than expected), weakness, and/ or discolored urine: obtain thorough history including infectious symptoms, recent exercise (and associated heat exposure), medications and/ or supplements
    - Obtain chemistry panel (including electrolytes, BUN, creatinine, liver enzymes), CK, urinalysis with microscopy, +/- urine myoglobin
    - Identify electrolyte abnormalities, obtain EKG if hyperkalemia. Correct only symptomatic hypocalcemia
    - Identify AKI as 1.5x baseline creatinine or higher (KDIGO)
        - When baseline creatinine in last 6 months unknown, back calculation using modified bedside Schwartz equation can approximate baseline creatinine (serum creatinine in mg/dl = 120 x 0.413 / height in cm), assuming normal GFR 120 ml/min per 1.73 m2 (Staples)
    - Discontinue any potential inciting agents (over 100 associated medications)
    - Screen uric acid levels, potentially treat based on level (off-label use, rasburicase) (Lin)
    - Recommend nephrology sub- specialist consultation if refractory hyperkalemia, severe hyperphosphatemia, fluid overload/ oliguria, significant acute kidney injury
- Consider inpatient admission for patients with CK > 5000 U/L given increased association with AKI above this level in adults (Brown)
    - Consider admission if elevated CK (below 5000 U/L) AND inability to tolerate fluids, inability to ambulate, or electrolyte concerns/ kidney injury
        - In pediatric trauma patients, AKI associated with CK levels above 3000 U/L given risks such as hemodynamic instability and contrast exposure (Talving)
    - CK peaks slowly compared to myoglobin, and early presentation may miss diagnosis. If clinical suspicion for severe disease, consider fluid resuscitation and repeat CK level in 8-12 hours
    - If no kidney injury, no electrolyte abnormalities, CK level < 5000, and ability to tolerate oral intake goals, can consider outpatient management with close follow-up
- For admitted patients, consider IV fluid bolus (1-2x) and then continuous IV fluids at TWICE maintenance fluid rate (no consensus pediatric guideline on type or rate of fluid). Can run up to 200-250 ml/hr although higher rates may be indicated based on patient size and unit policies.
    - Fluid delivery should be initiated within 6 hours of injury (Scharman)
    - Strictly monitor intake/ output, obtain daily weights
    - Closely monitor for fluid overload and decrease fluid delivery if hypervolemic

    - Obtain chemistry panel, CK at least 1-2x daily
    - Avoid NSAIDs
    - Encourage bedrest (avoid further injury)
    - No evidence to support bicarbonate supplantation (forced urinary alkalinization); may consider adding bicarbonate to fluids if patient acidotic although must balance risk worsening hypocalcemia
    - No evidence to support efficacy of mannitol to promote diuresis
    - Consult Nephrology as needed if AKI, electrolyte abnormalities or other questions
- No evidence- based guidance exists on threshold for discontinuation of aggressive hydration but may consider once CK below 5000 U/L
    - When CK below 5000 U/L, consider discharge once myalgias/ weakness markedly improved, tolerating good oral intake, having good urine output, normal renal function, and no electrolyte concerns with follow-up plan established
    - Referral to Sports Medicine or Primary Care Provider for return to play
- After discharge, monitor chemistry panel, CK, UA in around 2-3 days
    - If CK remains >1000, continue check CK, BMP, UA weekly.
    - If CK remains elevated for several weeks, refer to Pediatric Neurology for diagnostic work-up for underlying predisposition
    - If ongoing elevated creatinine, consider Nephrology referral.

Return to Play for Exertional Rhabdomyolysis

- Evaluate for high-risk criteria (Table 1) and refer for evaluation by myopathy specialist
- Return to Play should occur in a graduated fashion based on labs and clinical symptoms based on risk status (absence of high-risk criteria). No evidence-based guidelines exist. A three-phase guideline published by a military workgroup (CHAMP algorithm, http://champ.usushs.mil) provides a conservative approach (Table 2).
    - No evidence- based guideline for frequency of lab monitoring
        - Consider labs (CK, UA, BMP) within days after discharge. If normal, consider obtain one week after resumption of light activity (phase 2).
        - May consider repeat in 3-4 weeks before full return to sport.
    - Duration of gradual return to full sport suggested at least 4 weeks, although individualized plan should be developed
    - Analgesics (acetaminophen, ibuprofen) should be avoided to avoid masking pain

TABLE 1. High Risk Indicators: "RHABDO" mnemonic
R – Recurrent episodes **H –** High CK for many weeks episode despite rest **A –** Absence of intense or unaccustomed exercise (not a "too much, too fast, too soon" situation) **B –** Blood CK above 50x upper limit of normal **D –** Drugs, toxins, supplements or concomitant infection cannot explain the severity **O –** Other family members with history of ER, recurrent muscle cramps, malignant hyperthermia
Adapted from Scalco et al, 2016, *BMJ Open Sport Exerc*

TABLE 2. Return to Play Guidelines
Phase 1 - Rest, avoid resistance training - Repeat CK, UA, BMP 2-3 days after discharge, and then every 3-7 days. Once CK less than 5x ULN, can progress to Phase 2. Phase 2 - Begin light activity (no strenuous exercise) - Follow-up weekly with provider - If no clinical symptoms, can progress to Phase 3 Phase 3 - Gradual return to sport/ activity
Adapted from O'Connor et. al. *Curr. Sports Med. Rep.* 7:328-331

Reference

1. Al-Ismaili Z., Piccioni M, Zappitelli M. (2011) Rhabdomyolysis: pathogenesis of renal injury and management. *Pediatr Nephrol* 26:1781-1788
2. Brown CV, Rhee P, Chan L, et. al. (2004) Preventing renal failure in patiehts with rhabdomyolysis: do bicarbonate and mannitol make a difference? *J Trauma* 56:1191-1196
3. Friedman L, Wolfgruber H, Matloff R (2018) Rhabodmyolysis Clinical Pathway, Connecticut Children's Hospital. Available from https://www.connecticutchildrens.org/clinical-pathways/rhabdomyolysis/ Accessed March 2, 2022.
4. Gardner HM, Ashkenazi DJ, Hoefert JA, et. al. (2021) Acute Kidney Injury Among Children Admitted with Viral Rhabdomyolysis. *Hosp Pediatr* 11:878-885
5. Gelbart B, DeMarco R, Hussey AD, et. al. (2018) Rhabdomyolysis in a Tertiary PICU: A 10-Year Study. *Pediatr Crit Care Med* 19:e51-e57
6. Kellum JA, Lameire, et. al. (2013) KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). *Crit Care* 17:204
7. Lin P-Y, Lin C-C, Liu H-C, et. al. (2011) Rasburicase improves hyperuricemia in patients with acute kidney injury secondary to rhabdomyolysis caused by ecstasy intoxication and exertional heat strok. Pediatr Crit Care Med, 12(6):e424-7.
8. Mannix M, Tan ML, Wright R, et. al. (2006) Acute Pediatric Rhabdomyolysis: Causes and Rates of Renal Failure. *Pediatrics* 118:2119-2125
9. McMahon GM, Zeng X, Waikar SS. (2013) A risk prediction score for kidney failure or mortality in rhabdomyolysis. *JAMA Intern Med.* 173:1821-8
10. Naik RP, Smith-Whitley K, Hassell KL, et. al. (2018) Clinical Outcomes Associated With Sickle Cell Trait
11. NCAA Sport Medicine Handbook, 2014-2015. Available from https://www.ncaapublications.com/p-4374-2014-15-ncaa-sports-medicine-handbook.aspx Accessed March 2, 2022.
12. Nelson DA, Deuster PA, Carter R et. al. 2016) (Sickle Cell Trait, Rhabdomyolysis, and Mortality among U.S. Army Soldiers. *N Engl J Med*375:435-42
13. O'Connor FG, Brennan FH, Campbell W, et. al. (2008) Return to Physical Activity After Exertional Rhabdomyolysis. *Curr. Sports Med. Rep.* 7:328-331
14. O'Connor GFR, Deuster P, Leggit J, et. al. (2020) Clinical practice guidelines for the management of exertional rhabdomyolysis in warfighters. Available from https://champ.usuhs.edu/for-the-provider Accessed March 2, 2022.
15. Scalco R, Snoeck M, Quinlivan R, et. al. (2016) Exertional rhabdomyolysis: physiological response or manifestation of an underlying myopathy? *BMJ Open Sport Exerc* 2:e000151
16. Scharman EJ, Troutman WG. (2013) Prevention of Kidney Injury Following Rhabdomyolysis: A Systematic Review. *Ann Pharmacother* 47:90-105
17. Staples A, LeBlond R, Watkins S, et. al. (2010) *Pediatr Nephrol* 25:2321-2326
18. Szugye H (2020) Pediatric Rhabdomyolysis. *Pediatr Rev.* 41:265-275.
19. Talving P, Karamanos E, Skiada D, et. al. (2012) *J Trauma Acute Care Surg* 74:912-916
20. Tietze DC, Borchers J. (2014) Exertional Rhabdomyolysis in the Athlete: A Clinical Review. Sports Health 6:336-339
21. Yang Y, Carter LP, Cook RE, et. al. (2016) A case of exertional rhabdomyolysis: A cheer for standardizing inpatient management and prevention. 6:753-756.
22. Zepeda-Orozco D, Ault BH, Jones DP. Factors associated with acute renal failure in children with rhabdomyolysis. Pediatr Nephrol, 2008 Dec;23(12):2281-4.