Rhabdomyolysis and Myoglobin-Induced AKI

Andrew Bland, MD, FACP, FAAP

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Rhabdomyolysis and Myoglobin-Induced AKI: Student Handout

Learning Objectives

By the end of this handout, you should be able to: - Recognize clinical presentation and diagnostic criteria for rhabdomyolysis - Classify etiologies into traumatic, exertional, metabolic, and drug-induced categories - Understand the pathophysiology of myoglobin-induced acute kidney injury - Implement emergency management including aggressive hydration and urine alkalinization - Identify high-risk populations and prevention strategies - Recognize genetic myopathies presenting as exercise-induced rhabdomyolysis

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Definition and Diagnostic Criteria

Rhabdomyolysis: Breakdown of skeletal muscle with release of intracellular contents into systemic circulation.

Diagnostic Threshold: - **Creatine kinase (CK) >5× upper limit of normal** (typically >1000 IU/L, often >5000-10,000 IU/L in symptomatic cases) - Clinical symptoms: myalgia, weakness, dark urine (myoglobinuria) - May progress to life-threatening complications: AKI, electrolyte imbalances, DIC, compartment syndrome

Severity Spectrum: - Mild: CK 1000-5000 IU/L; usually self-limited - Moderate: CK 5000-50,000 IU/L; high AKI risk - Severe: CK >50,000 IU/L; almost always requires ICU management

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Classification of Etiologies

1. Traumatic Rhabdomyolysis

Mechanisms: - Crush injuries from accidents, natural disasters, collapses - Prolonged immobilization (patient lying on limb for hours) - Compartment syndrome (external compression exceeds perfusion pressure) - Extensive surgical procedures (particularly lengthy lithotomy or lateral positioning)

Clinical Recognition: - History of direct trauma or crush mechanism - Massive CK elevations (often >100,000 IU/L) - Rapid AKI development within 24-48 hours - Gross myoglobinuria (cola-colored urine)

Prevention in Surgical Setting: - Frequent position changes (if prolonged procedures) - Padding of pressure points - Early mobilization post-op - Adequate hydration peri-operatively

2. Exertional Rhabdomyolysis

Triggers: - Unaccustomed intense exercise (military training, competitive athletics) - Prolonged exercise in hot conditions - Exercise combined with dehydration - Exercise combined with heat stress and high humidity

Classic Scenario: - Young person (typically male) engages in unusual intense physical activity - Develops muscle pain, weakness, dark urine during or shortly after exercise - CK markedly elevated - Risk factors: dehydration, heat, lack of acclimatization

Underlying Factors Increasing Risk: - Sickle cell disease (can precipitate rhabdo with exertion) - Unrecognized metabolic myopathy - Anticholinergic medications (impair sweating) - High environmental temperature + humidity

Prevention: - Gradual acclimatization to exercise (5-14 day period) - Adequate hydration before, during, and after exercise - Recognition of warning signs (severe cramping, dark urine) - Cool-off periods in heat

3. Metabolic and Genetic Causes

Glycogen Storage Diseases: - McArdle disease (GSD V): Muscle phosphorylase deficiency - Exercise-induced rhabdo - Characteristic “second wind” (symptoms improve 10-15 min into exercise as alternative fuels become available) - Tarui disease (GSD VII): Phosphofructokinase deficiency - Exercise intolerance, myoglobinuria - Associated hemolytic anemia (same enzyme deficiency in RBCs)

Fatty Acid Oxidation Defects: - CPT II deficiency: Most common cause of **recurrent exertional rhabdomyolysis** in adults - Triggered by prolonged exercise, cold exposure, or fasting - Temperature-sensitive enzyme (cold worsens symptoms) - Multiple episodes over years

Mitochondrial Disorders: - Impaired oxidative phosphorylation - Variable presentations - Exercise intolerance - May manifest with heat sensitivity

Ion Channel Disorders: - RYR1 mutations: Can cause exercise/heat-induced rhabdomyolysis - Periodic paralyses: May present with rhabdo during attacks

Clinical Pearl: Recurrent exertional rhabdo in young adults (especially triggered by specific conditions like cold or fasting) should prompt genetic evaluation.

4. Drug and Toxin-Induced

Statins: - Most common medication cause - Risk increased with: higher doses, drug interactions (especially with CYP3A4 inhibitors), renal impairment - May occur weeks to months after initiation - Immune-mediated myopathy possible

Alcohols: - Ethanol (direct myotoxicity + immobilization + electrolyte disturbances) - Methanol and ethylene glycol (toxic metabolites)

Stimulants and Drugs of Abuse: - Cocaine (severe vasoconstriction compromising muscle perfusion) - Amphetamines (hyperthermia, agitation, muscle hyperactivity) - Heroin (immobilization, direct toxicity) - MDMA/Ecstasy (hyperthermia, exertion, dehydration)

Daptomycin (Antibiotic): - Rare cause of drug-induced rhabdo - Risk increases with high doses, prolonged therapy, renal impairment - May cause creatine kinase elevation without overt rhabdo

Corticosteroids: - Particularly with high doses or rapid escalation - Myopathy may be vacuolar (affects proximal muscles) - Distinguish from rhabdo per se (less severe CK elevation)

Hyperthermia-Inducing Agents: - Anticholinergics (impair sweating) - Neuroleptic malignant syndrome (antipsychotics + dopamine antagonists) - Malignant hyperthermia (anesthetic-related)

Pathophysiology of Myoglobin-Induced AKI

The Myoglobin Cascade

1. **Muscle Injury** ☐ Release of intracellular contents
2. **Myoglobin Release** ☐ Large myoglobin molecules exceed renal threshold for reabsorption
3. **Myoglobinuria** ☐ Dark ("cola" or "tea-colored") urine
4. **Myoglobin Precipitation** ☐ In acidic urine (pH <5.6), myoglobin polymerizes
5. **Tubular Obstruction** ☐ Precipitated myoglobin blocks tubular flow
6. **Tubular Injury** ☐ Direct toxicity from oxidative stress, heme iron release
7. **Acute Tubular Necrosis** ☐ Tubular epithelial cell necrosis
8. **Acute Kidney Injury** ☐ Oliguria, rising creatinine

Additional Contributing Factors

Hypovolemia: - Myoglobin precipitation increases urine concentration - Volume depletion from third-spacing (rhabdo causes massive intracellular fluid sequestration, can lose 40% of body water) - Hypotension reduces renal perfusion

Electrolyte Disturbances: - **Hyperkalemia:** From massive cell death - **Hyperphosphatemia:** From cell contents release - **Hypocalcemia (phase 1):** Calcium binds to damaged muscle - **Hypercalcemia (recovery phase):** Calcium mobilizes from injured muscle

DIC Risk: - Tissue factor released from muscle - Can trigger disseminated intravascular coagulation - Associated with severe rhabdo and worst outcomes

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Clinical Recognition and Laboratory Diagnosis

Clinical Presentation

Acute Phase (During/Immediately After Muscle Injury): - Severe myalgia (muscle pain) - Muscle weakness or immobility - Dark/cola-colored urine (myoglobinuria) - Nausea, vomiting (from hyperkalemia or toxemia) - Oliguria or anuria

Later Manifestations: - Rising creatinine (may lag CK peak by 24-48 hours) - Hyperkalemia symptoms: palpitations, weakness, cardiac arrhythmias - Hypocalcemia symptoms: tetany, paresthesias (if severe) - Edema and compartment syndrome (if localized crush injury)

Laboratory Diagnosis

Gold Standard Marker: - **Creatine kinase (CK)** — reflects muscle injury magnitude - Peak CK typically occurs 24-72 hours after injury - CK >100,000 IU/L indicates severe injury with very high AKI risk - CK rise faster than creatinine rise (diagnostic timing advantage)

Confirmation of Myoglobinuria: - **Urine dipstick:** Positive for "blood" (actually detects myoglobin/hemoglobin) - **Urine microscopy:** NO RBCs despite positive dipstick = myoglobinuria - This discordance (positive blood dipstick + RBC-negative urinalysis) is classic - **Serum myoglobin:** Elevated (not routinely measured; less practical than CK)

Additional Labs: | Test | Finding | Significance | |——|———|—| | Potassium | Often >5.5-7.0 mEq/L | Life-threatening arrhythmia risk | | Phosphate | Elevated | Reflects massive cell death | | Calcium (acute) | Low | Binds to damaged muscle | | BUN/Creatinine | Rising | Indicates developing AKI | | LDH | Markedly elevated | Reflects muscle and hemolysis | | Uric acid | Elevated | From nucleic acid metabolism | | Creatinine | Progressive rise | Peak lags CK peak by 24-48 hrs |

Urine Findings: - Dark brown/cola color - Positive dipstick for blood without RBCs (myoglobin) - May have muddy brown casts (cellular debris) - pH typically <6.0 (predisposes to myoglobin precipitation)

Distinguishing Features from Other Hemoglobinurias

Source	Urine Color	Dipstick	RBCs on Microscopy	Clinical Clue
Myoglobin (rhabdo)	Dark cola-brown	Positive	NEGATIVE	History of muscle injury; very high CK
Hemoglobin (hemolysis)	Tea-brown	Positive	NEGATIVE	Elevated indirect bilirubin, LDH; low haptoglobin
Hematuria (blood)	Red/pink	Positive	POSITIVE	RBCs visualized on microscopy

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Emergency Management

Phase 1: Aggressive Fluid Resuscitation (Hours 0-24)

Goal: Maintain urine output 200-300 mL/hour to prevent myoglobin precipitation.

Method: 1. **Initial IV access:** Two large-bore IVs (central line if severe/anuric) 2. **Aggressive isotonic crystalloid (normal saline):** - Initial bolus: 1-1.5 L over first hour - Then: Target urine output 200-300 mL/hour - May require 10-15 L in first 24 hours 3. **Monitor closely:** - Urine output hourly - Vital signs and perfusion status - Electrolytes frequently (especially K+)

Rationale: - Dilutes myoglobin concentration in tubular fluid - Maintains glomerular filtration (reduces myoglobin precipitation risk) - Prevents hypovolemic shock from third-spacing

Complication Risk: Fluid overload, pulmonary edema (especially if AKI develops). Balance between aggressive resuscitation and avoiding pulmonary edema requires careful monitoring.

Phase 2: Urine Alkalinization (Controversial but Often Recommended)

Rationale: Myoglobin precipitates in acidic urine (pH <5.6); alkaline urine increases solubility.

Method (if pH <6.5): 1. **Add sodium bicarbonate to IV fluids:** - Target urine pH 6.5-8.0 - Typical: 50-100 mEq sodium bicarbonate in 1 L normal saline - Infuse at rate to achieve target urine pH 2. **Monitor:** - Urine pH frequently (goal >6.5) - Serum electrolytes (hypokalemia risk, hyponatremia risk) - Avoid overcorrection to pH >8.5 (increases other precipitation risks)

Evidence Level: Some controversy remains; benefit most clear in severe rhabdo (CK >20,000-50,000 IU/L).

Phase 3: Electrolyte Management

Hyperkalemia (Most Immediate Threat): - **Monitor:** EKG for peaked T waves, prolonged PR - **Treat if symptomatic or K+ >5.5-6.0 mEq/L:** - Calcium gluconate 10 mL of 10% IV (cardiac membrane stabilization) - Insulin + dextrose (shifts K+ intracellularly) - Albuterol nebulized (shifts K+ intracellularly) - Loop diuretics with aggressive hydration - Renal replacement therapy if medical management fails

Hypocalcemia: - Usually do NOT treat acute hypocalcemia (calcium binds to damaged muscle; treating may worsen outcomes during recovery phase) - May treat if symptomatic (tetany, seizures) with calcium gluconate - Monitor for hypercalcemia during recovery

Hyperphosphatemia: - Usually self-limited - Monitor for secondary hyperparathyroidism during recovery

Phase 4: Acute Kidney Injury Management

If AKI Develops Despite Fluid Resuscitation: 1. **Renal replacement therapy indications:** - Oliguria refractory to fluid challenge - K+ >6.0 mEq/L unresponsive to medical therapy - Pulmonary edema or fluid overload - Severe metabolic acidosis - Uremic symptoms

2. **Type of RRT:** Continuous modalities often preferred (gentler on hemodynamics, better electrolyte control)
3. **Dialysate:** Careful electrolyte composition (hyperkalemia, hypocalcemia risk)

Long-Term Management and Prevention

During Recovery Phase

- Continue hydration, electrolyte monitoring
- Monitor for **recovery phase hypercalcemia** (calcium mobilizes from muscle)
- Gradual activity advancement as CK decreases
- Repeat CK until normalized

Prevention in At-Risk Populations

For Exertional Rhabdo Risk: - Gradual acclimatization (5-14 day period) before intense exercise - Adequate hydration and electrolyte intake - Avoid combined heat/humidity/intensity extremes - Education on warning signs

For Genetic Myopathies: - Genetic counseling and testing for familial recurrent rhabdo - Avoid specific triggers (cold, fasting, prolonged exercise) - Prophylactic measures (carbohydrate loading, frequent meals)

For Drug-Induced: - Regular CK monitoring in patients on statins or other myotoxic agents - Educate about myalgia symptoms requiring CK check - Avoid drug combinations that increase statin myotoxicity

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Practice Questions

Question 1: A 24-year-old military recruit develops severe bilateral calf pain and dark urine during a 10-mile run in 95°F heat on day 3 of basic training. CK is 48,000 IU/L. Urine dipstick: positive for blood. Urinalysis: no RBCs seen. Which is the most appropriate initial management? A) Start furosemide to increase urine output B) Aggressive IV normal saline to target urine output 200-300 mL/hour C) Observe; mild rhabdo is self-limited D) Electrophoresis to detect light chains

Answer: B) Aggressive IV normal saline to target urine output 200-300 mL/hour. The constellation of exertional rhabdo (CK 48,000), myoglobinuria (positive dipstick, RBC-negative), and dark urine indicates significant rhabdomyolysis with high AKI risk. Aggressive hydration is the cornerstone of management, preventing myoglobin precipitation in tubules. Furosemide would be counterproductive (causes volume depletion); light chain disease is unlikely in this acute exertional context.

Question 2: A 58-year-old with recurrent episodes of exercise-induced myoglobinuria every few years (triggered by prolonged exercise, especially in cold weather) is evaluated. CK elevations are moderate (8,000-15,000 IU/L). Which genetic defect should be highest on your differential? A) Dystrophinopathy (Duchenne muscular dystrophy) B) CPT II deficiency C) McArdle disease D) Statin myopathy

Answer: B) CPT II deficiency. This patient's presentation—recurrent exertional rhabdo in adulthood, triggered by **prolonged exercise and cold exposure**, with moderate (not massive) CK elevations—is classic for CPT II deficiency (carnitine palmitoyltransferase II). The adult form presents with exercise-induced symptoms, and the temperature sensitivity (cold worsens

symptoms) is characteristic. McArdle disease (choice C) would present with shorter exercise triggers and the "second wind" phenomenon.

Question 3: A 45-year-old develops rhabdomyolysis (CK 85,000) from crush injury. After aggressive resuscitation targeting urine output of 250 mL/hour, urine remains dark brown and pH is 5.3. Creatinine is rising (1.2 to 2.1 in 24 hours) despite adequate urine output. Which step should be added? A) Increase saline rate further B) Add sodium bicarbonate to IV fluids, target urine pH >6.5 C) Start furosemide D) Initiate immediate dialysis

Answer: B) Add sodium bicarbonate to IV fluids, target urine pH >6.5. Despite adequate hydration, the acidic urine (pH 5.3) predisposes to myoglobin precipitation. Adding bicarbonate to raise urine pH >6.5 improves myoglobin solubility and may prevent further AKI progression. This is especially appropriate for severe rhabdo (CK 85,000). Dialysis may be needed if AKI worsens despite these measures, but medical optimization should continue first.

Key Takeaways

1. **CK >5× normal + dark urine = rhabdomyolysis diagnosis**
2. **Aggressive hydration is lifesaving** — target urine output 200-300 mL/hour
3. **Urine dipstick positive + NO RBCs = myoglobinuria** (classic discordance)
4. **Hyperkalemia is most immediately life-threatening** — EKG monitoring essential
5. **Urine alkalinization** helps prevent myoglobin precipitation in severe cases
6. **Recurrent exertional rhabdo** suggests genetic myopathy (CPT II, McArdle); genetic evaluation warranted
7. **Prevention** through acclimatization, hydration, recognition of warning signs is critical

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See Also

Related Student Handouts

- AKI Workup and Diagnostic Approach
- ATN Management
- Drug-Induced AKI
- Acid-Base Disorders
- Hyperkalemia Management

Clinical Content (01-Clinical-Medicine/Nephrology)

- AKI Hub - Full Clinical Reference
- Essential Renal Laboratory Tests

Atomic Notes (ZK)

- CRRT Principles

Butler-COM Resources

- Butler COM - Nephrology Deep Dive

Related Resources

- AKI Workup and Differential
- Comprehensive Rhabdomyolysis and Genetics
- Renal Replacement Therapy Basics

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