Rhabdomyolysis

November 25, 2016 by Josh Farkas

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Preamble

Rhabdomyolysis is a riddle wrapped in a mystery inside an enigma. The definition of rhabdomyolysis is debatable, specifically regarding which level of creatinine kinase (if any) predicts renal injury. There are precisely zero RCTs showing benefit of any treatment for rhabdomyolysis. So
from diagnosis to treatment, there is no solid evidence on this disease. This chapter attempts to cut a path through the confusion, but please be warned – little in this chapter is certain.

causes of rhabdomyolysis

物理损伤
- 创伤（尤其是压榨性损伤）
- 手术（尤其是血管或整形手术）
- 部分综合征
- 昏迷/昏迷伴有持续性不活动
- 缺血性肢
- 电击伤，烧伤

过度肌肉活动
- 癫痫
- 极端运动（例如马拉松、精神病、哮喘状态

体温异常
- 体温异常，尤其体温性肌病，例如抗精神病药物综合征
- 体温过低

电解质异常
- 低磷酸血症
- 低钙血症
- 低钾血症
- 高钠血症或低钠血症
- 高渗血症由于糖尿病酮症酸中毒或高渗高血糖非酮症综合征（HHNS）

药物/毒物
- 许多药物（重症监护室最突出的药物如下）
  - 他汀类和贝特类
  - 科尔奇辛
  - 抗精神病药物
  - 丙泊酚（有时通过丙泊酚给药综合征）
  - 达托霉素
- 毒理学
  - 激动剂（尤其是以高动力性）
  - 酒精（急性或慢性）

感染
- 多数，也许最常与：
  - 病毒感染（例如，流感、腺病毒、单纯疱疹病毒、 Epstein-Barr、Cytomegalovirus、HIV）
  - 肺炎链球菌，肺炎支原体
  - 肺炎链球菌
  - 中毒性休克综合征

其他
- 甲状腺功能亢进或减退
- 肢端皮炎，皮肌炎
Aside from creatinine kinase levels, three lab patterns may suggest rhabdomyolysis. None of these patterns are 100% sensitive, so they cannot be relied upon to diagnose rhabdomyolysis. However, if you happen to come across them, further investigation is warranted.

**pattern #1: tumor-lysis-syndrome pattern**
- Necrosis of large quantities of tissue may cause the following constellation of electrolyte changes. This is similar to tumor lysis syndrome:
  - Hyperkalemia
  - Hyperphosphatemia
  - Hypocalcemia (calcium enters damaged muscle cells, and also forms complexes with phosphate)
  - Elevated uric acid & lactate dehydrogenase levels (although these aren’t routinely measured)

**pattern #2: isolated AST (aspartate aminotransferase) elevation**
- Most elevations of AST (aspartate aminotransferase) reflect liver injury, and they are generally *accompanied* by an elevation of the ALT (alanine aminotransferase).
- Elevation of AST alone (or a dramatically elevated AST with minimally elevated ALT) raises a question of AST release from the *muscle* due to rhabdomyolysis.
**Rhabdomyolysis** - EMCrit Project

**pattern #3: urinalysis with positive “heme” but no red blood cells.**

- Free myoglobin released in the urine creates a paradoxical mismatch:
  - Myoglobin cross-reacts with the dipstick test for heme pigments. This will cause the urinalysis to be positive for "heme" or "blood."
  - Microscopic urinalysis shows no red blood cells (0-5 erythrocytes per high-powered field).
- Performance of urinalysis for diagnosis of rhabdomyolysis:
  - The sensitivity of a heme-positive urine is good (>90%) ([22082877](https://www.ncbi.nlm.nih.gov/pubmed/22082877), [24332910](https://www.ncbi.nlm.nih.gov/pubmed/24332910)). Patients with myoglobinuria may have heme-negative dipstick results (false-negative) due to highly concentrated urine, high nitrite concentrations, or ascorbic acid ([28235546](https://www.ncbi.nlm.nih.gov/pubmed/28235546)). Of course, the specificity of heme-positive urine is low.
  - The combination of heme-positive plus erythrocyte-negative urinalysis is seen only in ~35% of patients with rhabdomyolysis ([22082877](https://www.ncbi.nlm.nih.gov/pubmed/22082877), [24332910](https://www.ncbi.nlm.nih.gov/pubmed/24332910)).
- Clinical use of urinalysis to evaluate for rhabdomyolysis:
  - If you see the heme-positive, erythrocyte-negative pattern, then evaluate further for rhabdomyolysis or hemolysis.
  - If the urinalysis is heme-negative, this argues against rhabdomyolysis (without excluding it). Further evaluation may be indicated depending on your pre-test probability.

**signs & symptoms of rhabdomyolysis**

**symptoms**

- Overall in the literature, symptoms of rhabdomyolysis are uncommon ([30617905](https://www.ncbi.nlm.nih.gov/pubmed/30617905)).
  - Muscle pain (23% of patients)
  - Muscle weakness (12% of patients)
  - Muscle swelling
- Symptoms are usually absent in critically ill patients (e.g. due to sedation or altered sensorium).

**signs**

- True signs of rhabdomyolysis:
  - Brownish urine (“tea-colored”) is generally described as being reported in 5-10% of cases ([30630682](https://www.ncbi.nlm.nih.gov/pubmed/30630682)). However, this finding might be more noticeable among patients with foley catheters, in whom urine color is clinically apparent.
  - Red flags of possible muscle damage:
    - Patients who were comatose for prolonged periods may develop focal pressure ulceration or blistering on dependent skin. This should raise alertness for the possibility of underlying muscle damage.
    - Other signs of muscle damage (e.g. compartment syndrome or ischemic limb).
measuring CK levels to diagnose rhabdomyolysis

Rhabdomyolysis diagnosis (algorithm #1 of 2)

Check creatinine kinase level

- CK < 1,000 IU/L
  - Rhabdomyolysis currently absent
    - If CK mildly elevated & mechanism of injury places patient at high risk for rhabdomyolysis, may repeat in 8-12 hours.
  - Lower risk for acute kidney injury
    - Avoid nephrotoxins
    - Fluid resuscitate if severely hypovolemic
    - If concern may follow serial CK, labs, and McMahon score

- CK 1,000-5,000 IU/L
  - Mild rhabdomyolysis
    - (?) Clinical significance
  - Calculate McMahon rhabdomyolysis score
  - McMahon < 6
  - McMahon 6 or more
  - Treatment with fluid resuscitation (depending on hemodynamics)
    - See next algorithm

- CK > 5,000 IU/L
  - Moderate/severe rhabdomyolysis


when to check a creatinine kinase (CK) level?

- The above figure suggests some groups of patients in whom screening for rhabdomyolysis is reasonable.
- Given the lack of any proven therapy for rhabdomyolysis, it’s unclear how hard we should search for these cases.
do we need a repeat creatinine kinase (CK) level?

- Normal kinetics:
  - CK levels usually peak within ~24-48 hours and then gradually decline.
  - CK has a half-life of ~36 hours, whereas myoglobin has a half-life of ~2-4 hours ([28235546](https://www.ncbi.nlm.nih.gov/pubmed/28235546)).
- Serial CK values may be useful in some situations:
  - (a) Initial level is moderately elevated and there is a high index of suspicion for rhabdomyolysis.
  - (b) The initial CK level is 1,000-5,000 U/L. Further increase could indicate the need for fluid resuscitation (more on this below).
  - (c) Persistent CK may be a sign of compartment syndrome or ongoing myopathy (this doesn’t seem very useful clinically given the sluggish kinetics of CK – failure to clear CK would be a very delayed sign of tissue injury).

Rhabdomyolysis is extremely difficult to define precisely. Despite decades of research on this disease, there is no single consensus definition!

Reasons that rhabdomyolysis defies definition include the following:

- Rhabdomyolysis rarely occurs alone (e.g. it’s usually accompanied with traumatic injuries, shock, or hypoperfusion). This makes it extremely difficult to sort out the independent contribution of rhabdomyolysis to kidney failure.
Most studies of rhabdomyolysis have used creatinine levels to determine whether there is "renal failure." However, rhabdomyolysis may itself cause release of creatinine from myocytes and thereby directly increase the creatinine levels! This may create a circular logic loop, wherein elevated creatinine kinase and elevated creatinine are both measuring the same thing (muscle injury).

CK-based definition of rhabdomyolysis?

CK level is the cornerstone of rhabdomyolysis diagnosis. Unfortunately, CK level is problematic:

- CK level usually peaks 1-3 days after the initial injury. Waiting for the CK to reach a specific level before making the diagnosis of rhabdomyolysis will delay diagnosis.
- CK level correlates poorly with the risk of acute kidney injury and dialysis. This is probably because CK is only a surrogate measurement of myoglobin release (which is the true nephrotoxin).
- CK elevation can result from a massive myocardial infarction (but this is rare).

Nonetheless, CK is the standard biomarker for rhabdomyolysis. The following categorization scheme is consistent with the majority of current literature (30617905).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CK level</th>
<th>Clinical significance</th>
<th>Treatment needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CK level</td>
<td>~ 40-200 U/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild rhabdomyolysis</td>
<td>1,000-5,000 U/L</td>
<td>Low risk for kidney injury</td>
<td>Possibly Depends on context</td>
</tr>
<tr>
<td>Moderate rhabdomyolysis</td>
<td>5,000-15,000 U/L</td>
<td>Increased risk of renal injury</td>
<td>Yes</td>
</tr>
<tr>
<td>Severe rhabdomyolysis</td>
<td>&gt;15,000 U/L</td>
<td>Increased risk of dialysis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

McMahon Score

- Prognostic score generated from epidemiological data and labs available on admission.
- A score of six or greater indicates risk of acute kidney injury or dialysis, suggesting a possible benefit from treatment.

**Advantages of McMahon score**

- Doesn’t require waiting for CK to increase above 5,000 U/L prior to initiation of therapy.
- Based on better evidence than solely CK-based definitions:
  - Validated in two studies at different institutions (24000014, 27259093).
  - In one validation study, a McMahon score of 6 or greater had performance superior to CK > 5,000 U/L for the prediction of dialysis (McMahon had sensitivity and specificity of 86% and 68% respectively, whereas CK > 5,000 U/L had sensitivity and specificity of only 83% and 55%)/27259093.

**Rhabdomyolysis diagnosis** (algorithm #1 of 2)

- **Signs/symptoms**
  - Muscle pain
  - Tea-colored urine
- **High-risk situations for rhabdomyolysis**
  - Trauma, crush injury, compartment syndrome
  - Extreme exertion
  - Hyperthermia
  - Prolonged immobility
  - Intoxications
- **Isolated elevation of AST** (aspartate aminotransferase)
- **Suggestive urinalysis**
  - Hematuria
  - <5 RBCs
- **Evaluation of established acute kidney injury**

**Check creatinine kinase level**

- If CK < 1,000 IU/L
  - **Rhabdomyolysis currently absent**
  - If CK mildly elevated & mechanism of injury places patient at high risk for rhabdomyolysis, may repeat in 8-12 hours.
- If CK 1,000-5,000 IU/L
  - **Mild rhabdomyolysis**
    - ?? Clinical significance
- If CK > 5,000 IU/L
  - **Moderate/severe rhabdomyolysis**

**Lower risk for acute kidney injury**

- Avoid nephrotoxins
- Fluid resuscitate if severely hypovolemic
- If concern may follow serial CK, labs, and McMahon score

**McMahon score calculation**

- McMahon score < 6
  - McMahon 6 or more
  - **Calculate McMahon rhabdomyolysis score**
  - Treatment with fluid resuscitation (depending on hemodynamics)
    - See next algorithm

**Evaluate & treat any underlying problem(s)**

- Focused physical examination to evaluate for causes (e.g. compartment syndrome, ischemic limb).
- Discontinue any potentially causative medications.

**electrolyte management**

- *Hyperkalemia* due to renal failure and muscle breakdown may require urgent treatment.
  - More on treatment for hyperkalemia [here](https://emcrit.org/ibcc/hyperkalemia/).
- *Avoid* treatment of hypocalcemia if at possible (giving calcium may theoretically worsen muscle injury).
- Treat electrolyte abnormalities which may be contributing to rhabdomyolysis (especially hypokalemia and hypophosphatemia).
  - However, once *established* rhabdomyolysis occurs, these will often disappear due to potassium and phosphate release from muscle tissue.

**discontinue any nephrotoxic medications**

- The primary concern with rhabdomyolysis is the development of acute kidney injury.
- Discontinue any nephrotoxic medications.
- Consider holding or dose-reducing medications that may decrease renal perfusion (e.g. beta-blockers).

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**volume & pH management**

### who merits fluid therapy?

<table>
<thead>
<tr>
<th>CK &lt; 5,000</th>
<th>CK &gt; 5,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMahon &lt;6</td>
<td>- Definitely don't treat</td>
</tr>
<tr>
<td>McMahon 6 or higher</td>
<td>- Definitely treat</td>
</tr>
</tbody>
</table>

- Initiate treatment
- Consider stopping therapy in 24-48 hours if CK doesn't rise over 5,000.
- Current "standard of care" is to treat.
- May treat with lower volumes of fluid than usual.

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**when is fluid potentially indicated?**

- This can be roughly categorized as above.
- The most confusing box are patients with CK >5,000 U/L, yet a McMahon score <6
  - These patients are at low, yet finite risk of renal injury (the validation study by Simpson found that the McMahon score was only 86% sensitive for dialysis)\(^{(1)}\).
  - Some fluid therapy should be considered for these patients, but the benefit may be relatively lower.
- Some patients may have a CK of 1,000-5000 IU/L with a McMahon score of 6 or greater
  - This can occur early in the course of rhabdomyolysis, before the CK level has peaked.
  - Prompt initiation of fluid in these patients is reasonable, especially if myoglobin is detected (e.g. via urinalysis). Moderate fluid doses may be reasonable (e.g. lactated ringers at 150 ml/hr).
  - If the CK doesn't elevate to >5,000 U/L within 24-48 hours, the fluid therapy may be discontinued (the benefit of ongoing fluid therapy beyond 1-2 days is dubious anyway).

**volume of fluid?**

- It is generally believed that administration of fluid to flush myoglobin out of the renal tubules is beneficial treatment in rhabdomyolysis. There is probably some truth to this, but unfortunately the concept *hasn't* been studied prospectively. Most texts and review articles contain strong recommendations regarding precise volumes of fluid, which are completely arbitrary.
  - Three observational studies exist on the volume of fluid: two found that liberal fluid was beneficial whereas the other found that it was harmful \(^{(2)}\).
- Blind administration of large volume of fluid can provoke volume overload, which is harmful.
- The algorithm below seems sensible, but it's impossible to really know. 🤷

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Rhabdomyolysis - EMCrit Project

Rhabdomyolysis treatment

**Rhabdomyolysis (CK >1,000 U/L) with an indication for volume resuscitation:**
- CK >5,000 U/L
- McMahon score 6 or greater

### Clinical evaluation of volume status
- History (I/O balance, PO intake, weight changes)
- Physical exam, review of CXR or chest CT scan if available (Peripheral/pulmonary edema)
- Echocardiography

#### Hypovolemia
- Prompt resuscitation
- Volume challenge at ~150-200 ml/hour
  - Lytes normal (most patients): Lactated Ringers or Plasmalyte
  - Non-anion gap metabolic acidosis (NAGMA): Isotonic bicarbonate

#### Euvolemia
- Continue fluid infusion
  - Follow I/O balance carefully.
  - Stop fluid if patient begins running substantially not positive.

#### Hypovolemia
- ALL STOP
  - Don't give fluid.
  - If patient is severely congested, may consider gentle diuresis.

### What is the urine output over several hours?
- Good urine output
  - Patient is running net even or slightly positive
- Poor urine output
  - Patient is accumulating substantial volume (significantly net positive)

#### ALL STOP
- Do not give additional fluid.
- Inducing a state of volume overload may increase the risk of kidney injury.

---

**type of fluid?**

- Theoretically there may be some benefits to administration of bicarbonate to alkalinate the urine. However, studies haven't shown any benefit of isotonic bicarbonate compared to other fluids among all comers with rhabdomyolysis.
- For patients with relatively normal electrolytes, administration of lactated ringers or plasmalyte seems reasonable.
  - These fluids have relatively neutral effects on pH.
  - Some studies suggest that balanced crystalloids reduce the risk of acute kidney injury compared to normal saline.
- For patients with a non-anion-gap metabolic acidosis or uric acidosis, administration of isotonic bicarbonate is sensible:
  - Administration of isotonic bicarbonate to patients with a non-anion-gap metabolic acidosis makes physiologic sense in general and is usually accepted as therapy for this abnormality.
  - Treatment of uric acidosis with bicarbonate seemed to show renal benefit in the BICAR-ICU trial ([https://emcrit.org/pulmcrit/bicar-icu/](https://emcrit.org/pulmcrit/bicar-icu/)).

**when to stop fluid?**

- Most guidelines and texts recommend continuing fluid until the CK is below 5,000 U/L. This doesn't really make sense, though, because the CK persists for days after myoglobin is gone (and it is the myoglobin which is nephrotoxic; figure below).
  - Continuing fluid as long as the CK is >5,000 U/L amounts to treating a lab abnormality, rather than a true disease.
  - CK has a half-life of 36 hours. Thus, if the CK is markedly elevated, it will remain above 5,000 U/L for days – long after myoglobin is gone ([28235546](https://www.ncbi.nlm.nih.gov/pubmed/28235546)).
- Use your judgement regarding when to stop the fluid:
  - If the patient is running an even fluid balance (i.e. excreting all the fluid you give them), then infused fluid isn't causing harm. Continuing the fluid in this scenario is fine.
  - If the patient is running a *persistently positive* fluid balance, then fluid is accumulating and potentially causing harm. Consider earlier termination of fluid administration.
Historically, there was interest in using dialysis to remove myoglobin from the blood, but this hasn’t been shown to be effective.

- Dialysis should not be used “prophylactically” to prevent AKI.
- The indications for dialysis in these patients are the same as indications for dialysis in any patient.
  - For more on the use of dialysis in AKI, see the [AKI chapter](https://emcrit.org/ibcc/acute-kidney-injury/).

### algorithms

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Rhabdomyolysis (CK >1,000 U/L) with an indication for volume resuscitation:

! CK >5,000 U/L
! McMahon score 6 or greater

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- History (S I/O balance, PO intake, weight changes)
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- Echocardiography

Hypovolemia

Euvolemia

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Prompt resuscitation

Volume challenge at <150-200 ml/hour

Lytes normal (most patients): Lactated Ringers or PlasmaLyte
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What is the urine output over several hours?

Good urine output
Patient is running net even or slightly positive

Poor urine output
Patient is accumulating substantial volume (significantly net positive)

Continue fluid infusion

- Follow I/O balance carefully
- Stop fluid if patient begins running substantially net positive.

ALL STOP

- Don’t give fluid.
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ALL STOP

Do not give additional fluid. Inducing a state of volume overload may increase the risk of kidney injury.

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failure to review the medication list and discontinue all potentially causative drugs.
- Placing the patient on 200 ml/hour, forgetting about it, and discovering on the following day that the patient is five liters positive.
- Failure to discontinue nephrotoxic medications.

**Going further:**

- [Rhabdomyolysis](https://wikem.org/wiki/Rhabdomyolysis) (WikEM)

**Key references**


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The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.