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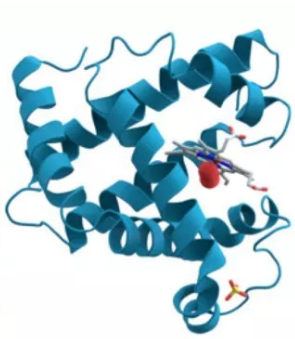
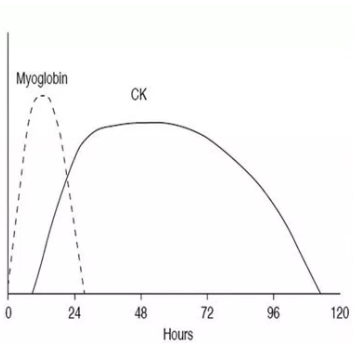
Rhabdomyolysis

November 25, 2016 by Josh Farkas

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Preamble

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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

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physical injury

- Trauma (especially crush injury)
- Surgery (especially vascular or orthopedic)
- Compartment syndrome
- Stupor/coma with prolonged immobility
- Ischemic limb
- Electrical injury, burns

excessive muscle activity

- Seizure
- Extreme exercise (e.g. marathon running, psychotic agitation, status asthmaticus)

dysthermia

- Hyperthermia of any etiology (especially hyperthermic rigidity syndromes, e.g. neuroleptic malignant syndrome)
- Hypothermia

electrolyte abnormalities

- hypoPhosphatemia
- hypoCalcemia
- hypoKalemia
- hypernatremia or hyponatremia
- hyperosmolarity due to diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic syndrome (HHNS)

medications / toxins

- *Many* medications (most notable offenders in ICU are as follows)
  - Statins & fibrates
  - Colchicine
  - Antipsychotics
  - Propofol (sometimes via propofol infusion syndrome)
  - Daptomycin
- Toxicology
  - Sympathomimetics (especially in combination with hyperactivity)
  - Alcohol (acute or chronic)

infections

- Numerous, perhaps most commonly associated with:
  - Viral infections (e.g., influenza, adenovirus, herpes simplex, Epstein-Barr, Cytomegalovirus, HIV)
  - Legionella, Mycoplasma pneumoniae
  - Clostridium spp.
  - Toxic shock syndrome

other

- Hyperthyroidism or hypothyroidism
- Dermatomyositis, polymyositis

lab clues to the diagnosis of rhabdomyolysis

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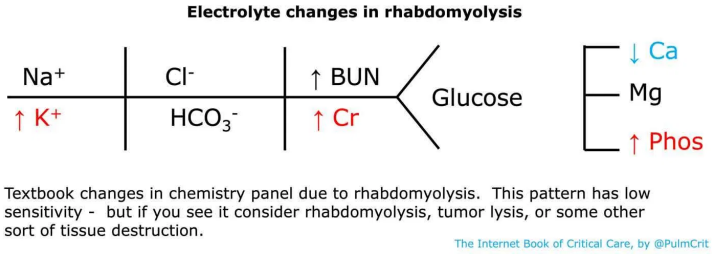
Aside from creatinine kinase levels, three lab patterns may suggest rhabdomyolysis. None of these patterns are 100% sensitive, so they cannot be relied upon to diagnose rhabdomyolysis. However, if you happen to come across them, further investigation is warranted.

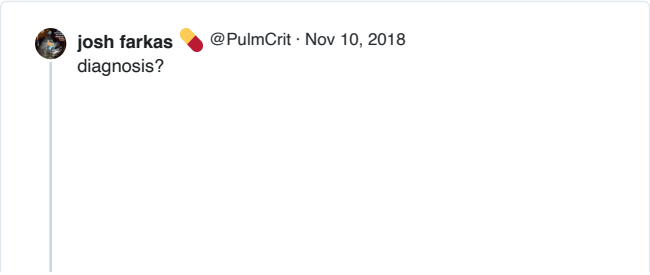


pattern #1: tumor-lysis-syndrome pattern

- Necrosis of large quantities of tissue may cause the following constellation of electrolyte changes. This is similiar 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.



URINALYSIS	
Color	Yellow
Clarity, UA	Clear
Refractometer SG,U...	1.033
pH, UA	6.0
Glucose, UA	Neg
Bilirubin, UA	Neg

Chris Nickson
@precordialthump

Myoglobinuria or haemoglobinuria

3 1:18 AM - Nov 11, 2018

See Chris Nickson's other Tweets

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.

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signs & symptoms of rhabdomyolysis

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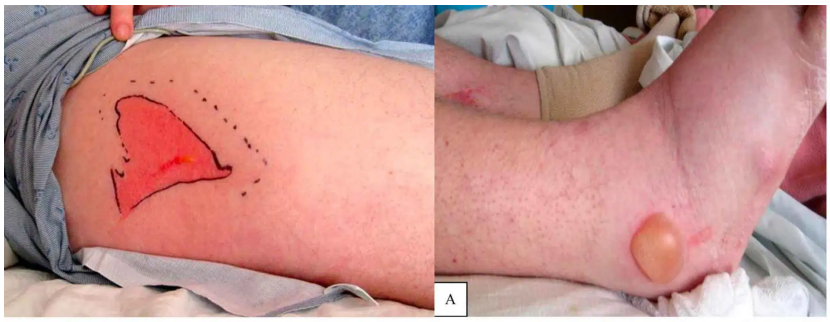
symptoms

- 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).



Drug intoxication leading to prolonged immobility may cause focal pressure ulceration (*left*) or blistering of the skin ("coma blisters," *right*). These aren't direct signs of rhabdomyolysis, but they should raise concern regarding injury to underlying muscle. This patient had rhabdomyolysis with a creatinine kinase of 33,000 U/L and mild acute kidney injury.
(Weigand TJ, Gorodetsky RM, Peredy TR, 2013, Asia Pac J Med Toxicol 2013; 2: 153-156)

measuring CK levels to diagnose rhabdomyolysis

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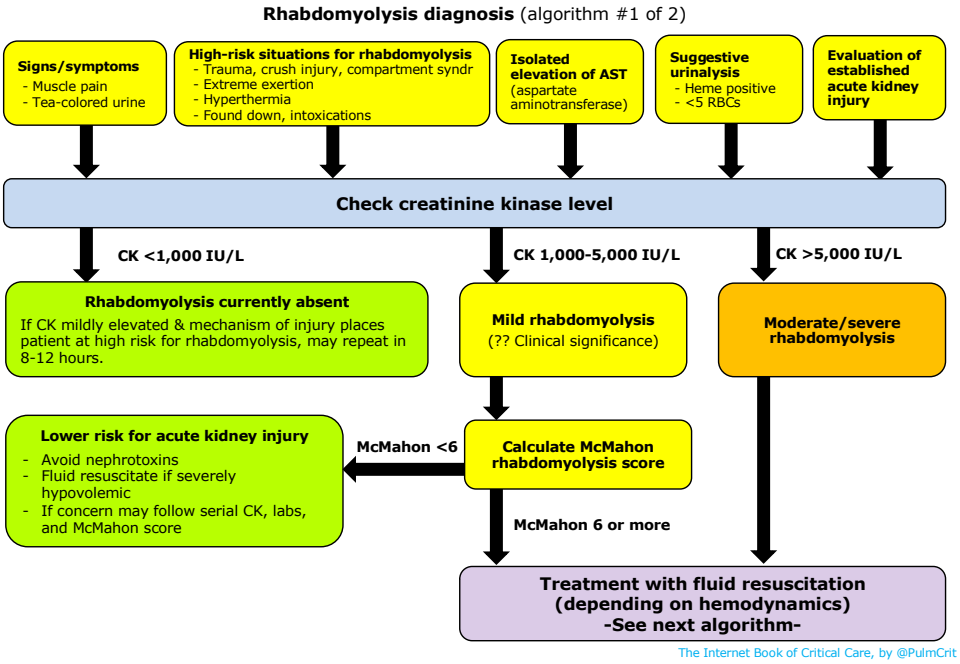

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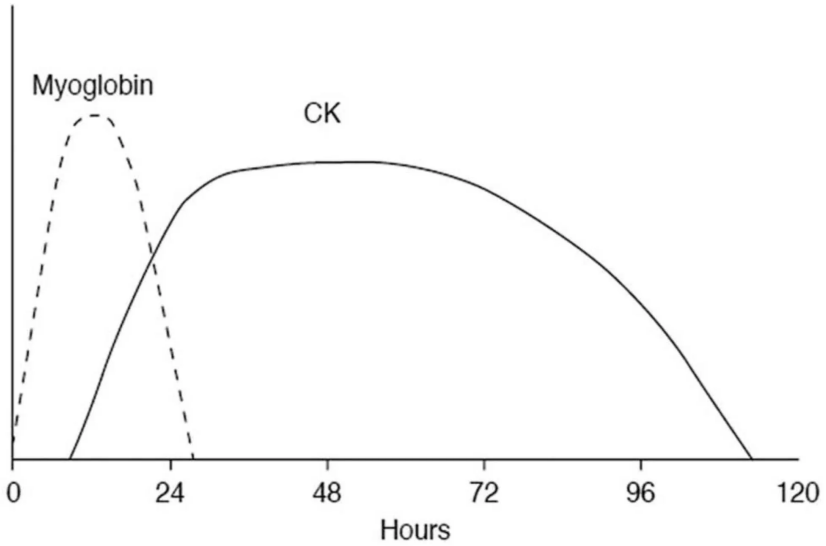
when to check a creatinine kinase (CK) level?

- 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.



Time-course of myoglobin and Creatinine Kinase (CK) elevation during rhabdomyolysis. CK is generally measured as the lab of choice for rhabdomyolysis, because it persists for longer. However, *myoglobin* is the molecule which is actually toxic to the kidneys (whereas CK merely acts as a marker of muscle injury).
Giannoglu GD et al. 2007 PMID 17338959

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).

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difficulty in defining rhabdomyolysis

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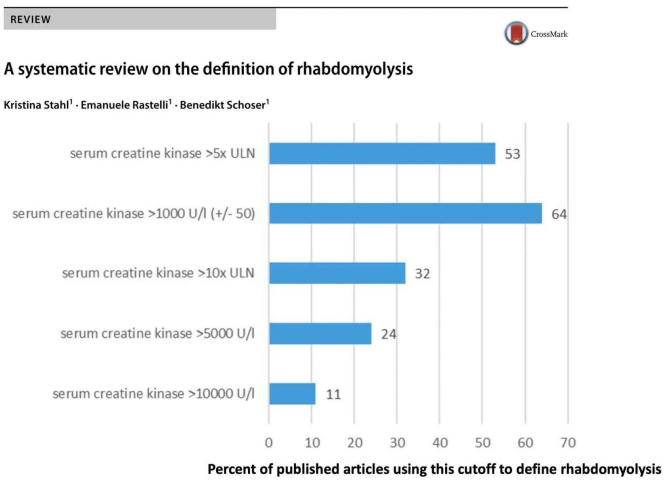

There is no consensus on the definition of rhabdomyolysis! The most popular definition is a CK >1,000 U/L or >5x the upper limit normal (which are fairly close).

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?

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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 (https://www.ncbi.nlm.nih.gov/pubmed/30617905)).

Definition of rhabdomyolysis (?)

Diagnosis	CK level	Clinical significance	Treatment needed
Normal CK level	~ 40-200 U/L		
Mild rhabdomyolysis	1,000-5,000 U/L	Low risk for kidney injury	Possibly Depends on context
Moderate rhabdomyolysis	5,000-15,000 U/L	Increased risk of renal injury	Yes
Severe rhabdomyolysis	>15,000 U/L	Increased risk of dialysis	Yes

The Internet Book of Critical Care, by @PulmCrit

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McMahon Score

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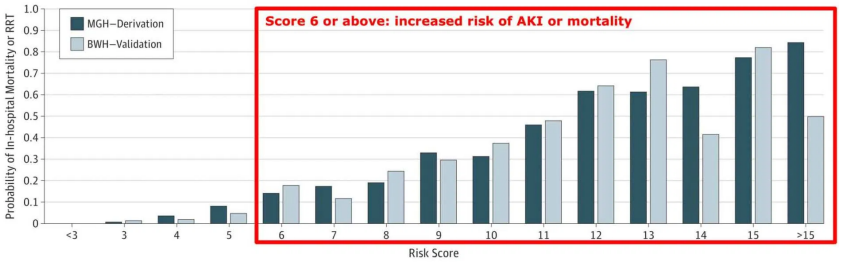
McMahon score basics [MDCalc link] (https://www.mdcalc.com/mcmahon-score-rhabdomyolysis)

- 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.

Figure 2. Probability of In-hospital Mortality or Acute Kidney Injury Requiring Renal Replacement Therapy



	<3	3	4	5	6	7	8	9	10	11	12	13	14	15	>15
Event rate	0	4	3	27	48	40	43	52	45	47	47	38	19	19	18
Patient count	130	358	105	387	307	269	203	164	134	101	75	57	34	24	23

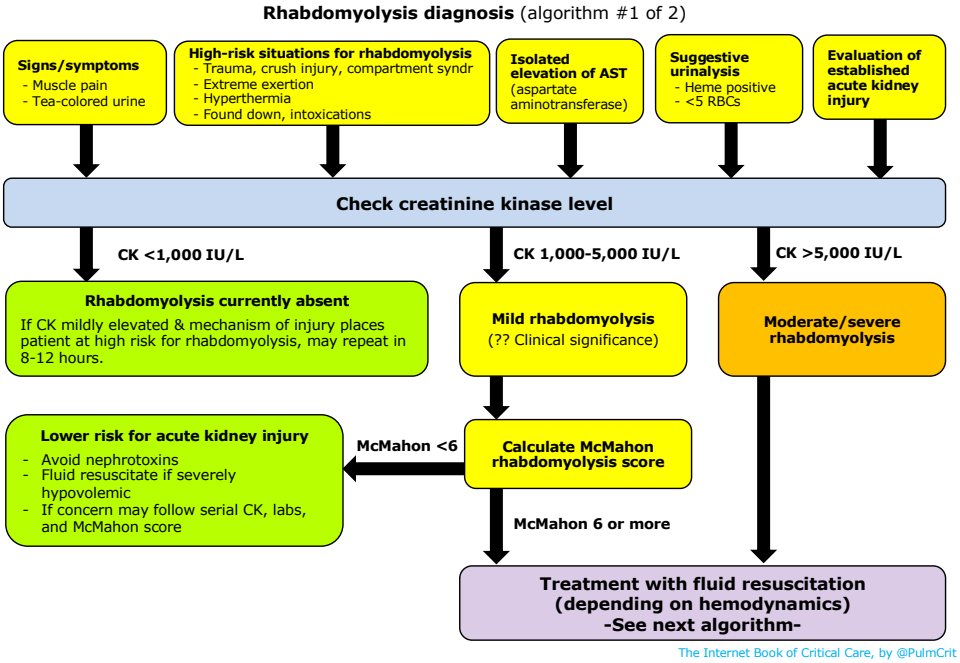
Dark blue bars and light blue bars show the observed risk at Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH), respectively. RRT indicates renal replacement therapy.

Derivation & validation of the McMahon score. Observed events include *all-cause* mortality and *all-cause* AKI. These will over-estimate the risk of rhabdomyolysis-induced mortality or AKI.

McMahon GM et al 2013; PMID 24000014

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 (https://www.ncbi.nlm.nih.gov/pubmed/24000014), 27259093 (https://www.ncbi.nlm.nih.gov/pubmed/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 (https://www.ncbi.nlm.nih.gov/pubmed/27259093)).



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treatment basics

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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

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who merits fluid therapy?

	McMahon <6	McMahon 6 or higher
CK < 5,000	- Definitely don't treat	- Initiate treatment - Consider stopping therapy in 24-48 hours if CK doesn't rise over 5,000.
CK > 5,000	- Debatable - Current "standard of care" is to treat. - May treat with lower volumes of fluid than usual.	- Definitely treat

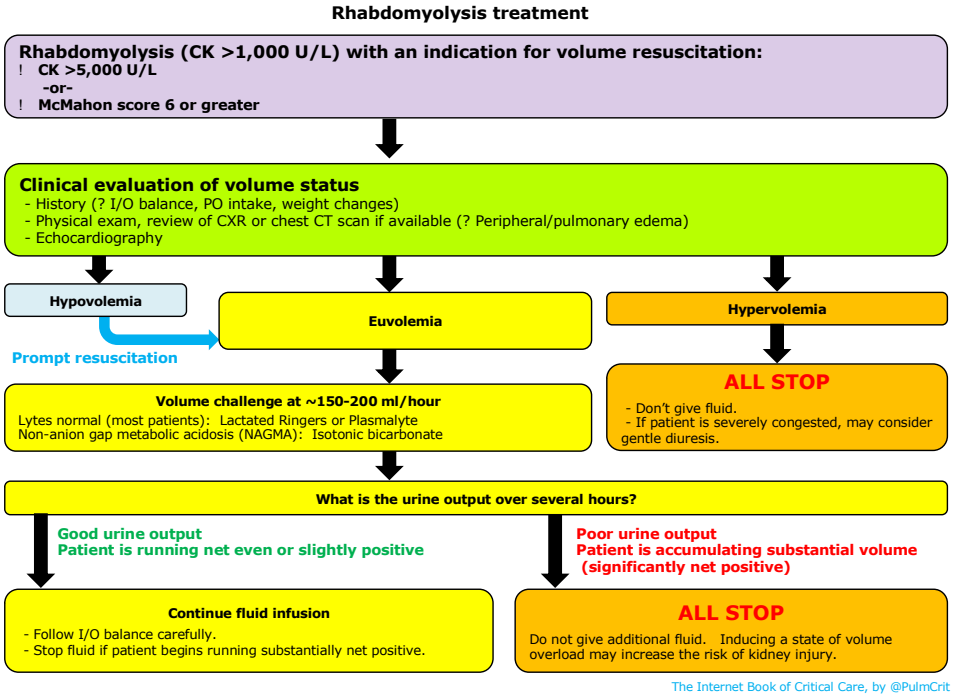
The Internet Book of Critical Care, by @PulmCrit

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)(27259093 (https://www.ncbi.nlm.nih.gov/pubmed/27259093)).
  - 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! (30644084 (https://www.ncbi.nlm.nih.gov/pubmed/30644084))
- 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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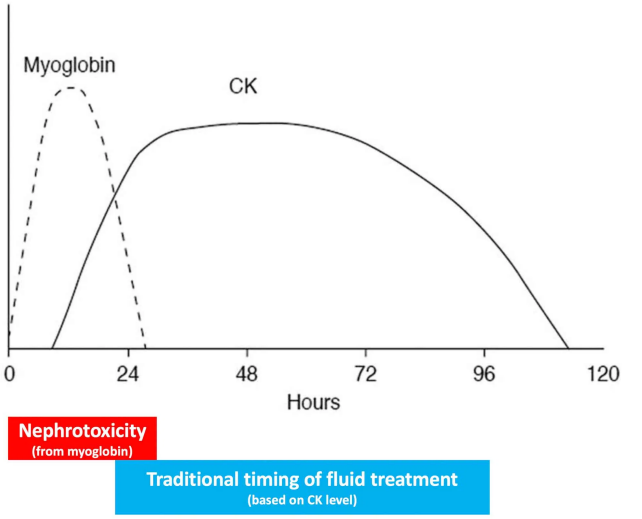
type of fluid?

- Theoretically there may be some benefits to administration of bicarbonate to alkalinize 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 uremic acidosis, administration of isotonic bicarbonate is sensible:
  - Administration of isotonic bicarbonate to patients with non-anion-gap metabolic acidosis makes physiologic sense in general and is usually accepted as therapy for this abnormality.
  - Treatment of uremic acidosis with bicarbonate seemed to show renal benefit in the BICAR-ICU trial (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.



Nephrotoxicity is due to myoglobin, which is cleared rapidly. Traditionally, fluid therapy has been provided as long as the CK level is above 5,000 U/L. This makes little sense, because it leads to *delayed* and *prolonged* fluid therapy (lasting for days after the renal insult has been removed).
Giannoglu GD et al. 2007 PMID 17338959

dialysis

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- 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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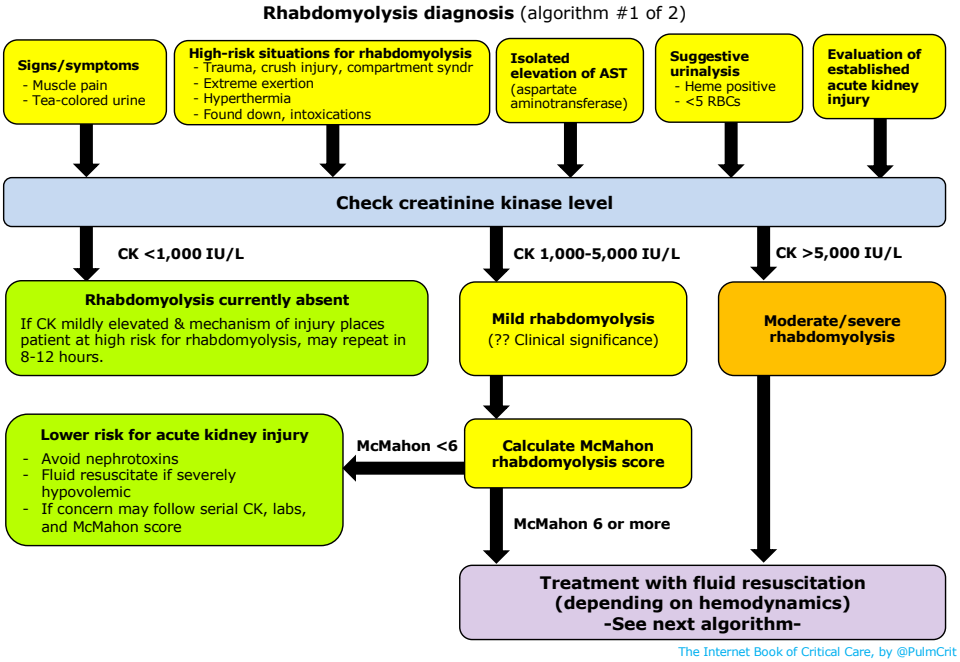

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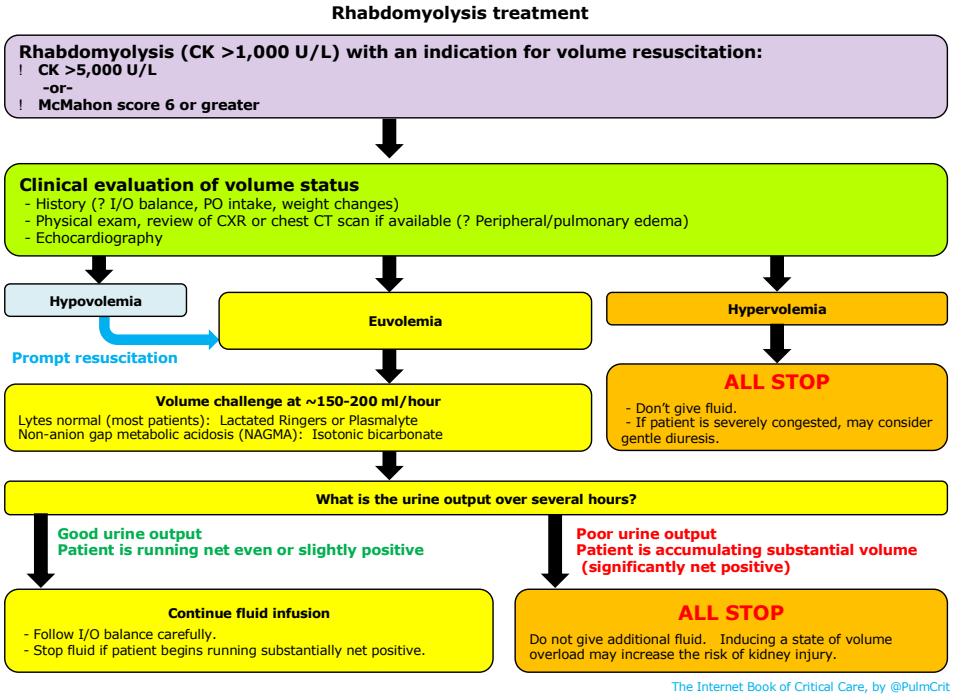

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podcast

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questions & discussion

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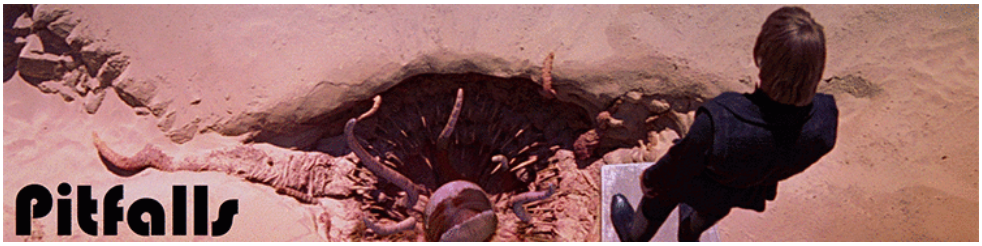

(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif)

- 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

- Michelsen J et al 2019: Prevention of rhabdomyolysis-induced acute kidney injury – a DASAIM/DSIT clinical practice guideline.
  - *Modern, evidence-based guideline to treatment of rhabdomyolysis. PubMed link here (https://www.ncbi.nlm.nih.gov/pubmed/30644084) ; PDF here (https://emcrit.org/wp-content/uploads/2016/11/Michelsen_et_al-2019-Acta_Anaesthesiologica_Scandinavica.pdf) . Spoiler alert: it doesn't make a lot of recommendations because no high-level evidence exists.*

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many FOAM sites including IBCC are currently in the process of upgrading to wordpress-Gutenberg. eventually the IBCC will be fully renovated (& hopefully better than before), but for now the formatting won't be perfect.

7 9:28 AM - May 14, 2019

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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.