Rhabdomyolysis and Acute Kidney Injury (AKI)

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Outline of talk

- Case presentations
- Causes, pathophysiology, and histology
- Diagnosis
- Course
- Treatment
- Applications to WSER

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Case reports

Case #1: A 19-year old college freshman experienced 2 episodes of rhabdomyolysis while playing competitive ultimate frisbee. The first episode occurred following a 5-hr frisbee tournament (her actual playing time was estimated to be 3 hours).
At the end of the tournament, she developed severe, diffuse muscle soreness. She was unable to straighten her elbows and knees and had difficulty standing because of soreness in her back muscles. Her urine became brown-colored but she did not seek medical attention. The muscle soreness resolved after 3 days.
Her second episode of rhabdomyolysis occurred 2 weeks later. This time, she participated in a 2-hr frisbee scrimmage followed by a 2-hr karate class. Shortly thereafter, she experienced severe muscle cramping and sought medical attention.
The following day, her CK (creatine kinase, an enzyme found in muscle cells) levels peaked at 59,000 U/L. Over the following week, the CK level fell to 266.
She did not recall any illness or fever preceding these 2 episodes and was not taking any medication. Until this point in her life, this young woman had no history of rhabdomyolysis. In high school, she played tennis and ran track. She tolerated workouts of up to 2 hours without difficulty. She was a sprinter, but could run 2 miles with no problem. It was subsequently determined that she had a genetic predisposition for rhabdomyolysis (Krivickas LS. 2006).

• **Case #2:** A 40-year old AA male developed rhabdomyolysis in his biceps after doing several sets of "negative curls". These are exercises where a spotter helps lift a heavy barbell up (concentric phase), and then the weight-lifter lowers the barbell (without assistance) until his arms are in an extended position (eccentric phase). Roughly 18 hours after doing negative curls, this athlete experienced severe biceps pain and could not fully extend his arms. His CK levels reached 76,000 U/L (normal range: 60-320 U/L) (Bolgiano EB. 1994).

• **Case #3:** A 21-year old inmate participated in a prison hazing ritual where he had to move 10 chess pieces on the floor (didn't use his hands…). The chess pieces were lined up on the floor and the prisoner had to squat to first pick them up, then had to squat again to put them down. This required approximately 110 deep knee bends.

Within 12 hours, he was unable to leave his bed because of severe pain in his anterior thighs. Three days later, he was taken to the hospital with complaints of brown urine and nocturia. On physical exam, his thighs were mildly swollen and his quadriceps were exquisitely tender. He was unable to flex his knees. He had protein in his urine, and his CK level was greater than 160,000 U/L. With treatment, the CK levels returned to normal after 12 days (Frucht M. 1994).

Rhabdomyolysis: Nature's way of telling you to stop f***ing running already.

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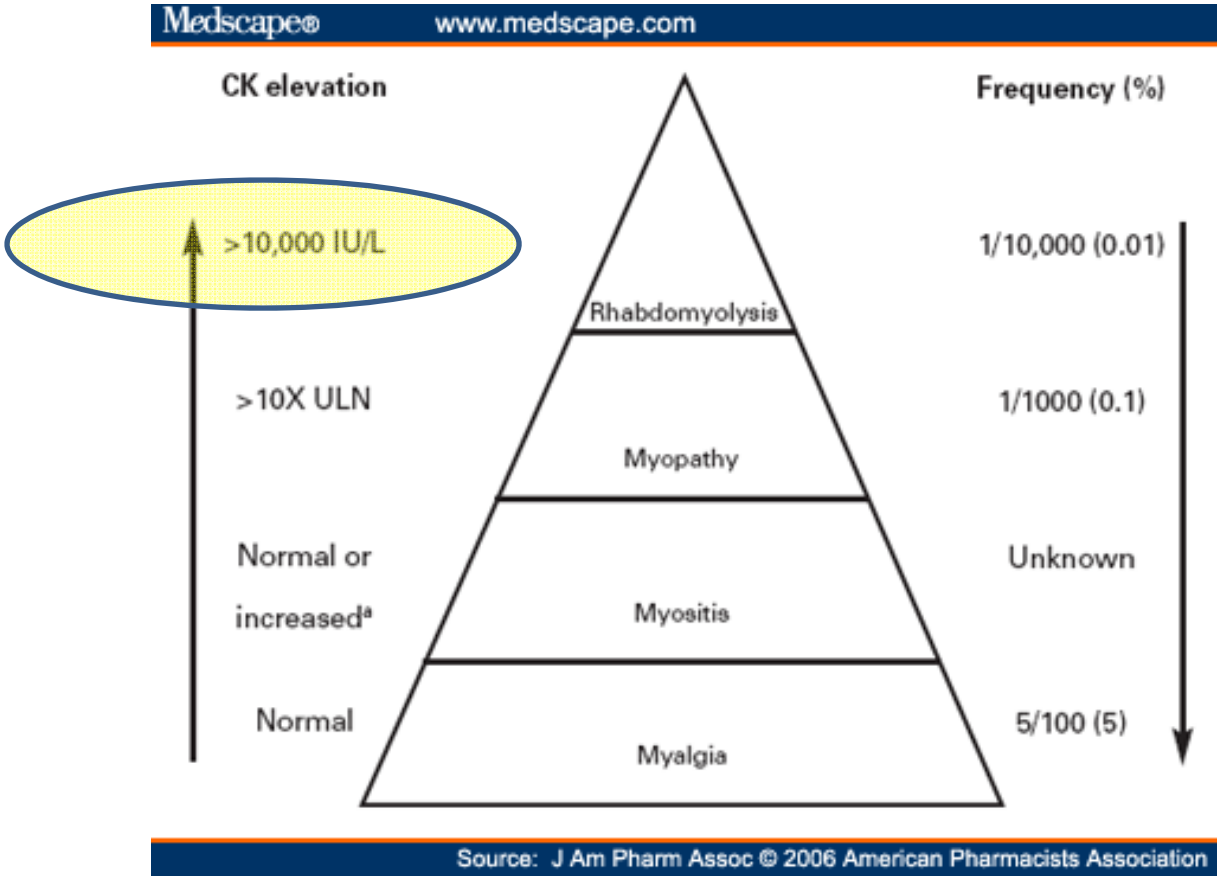
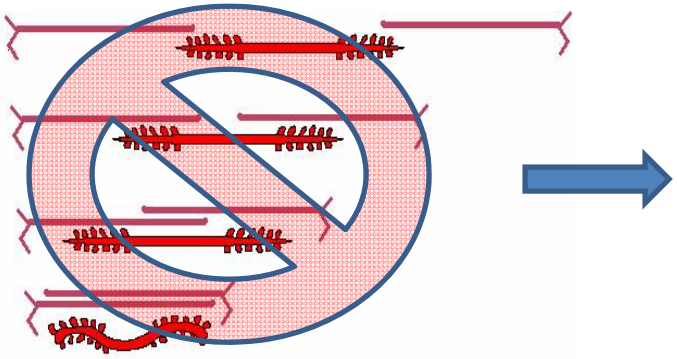
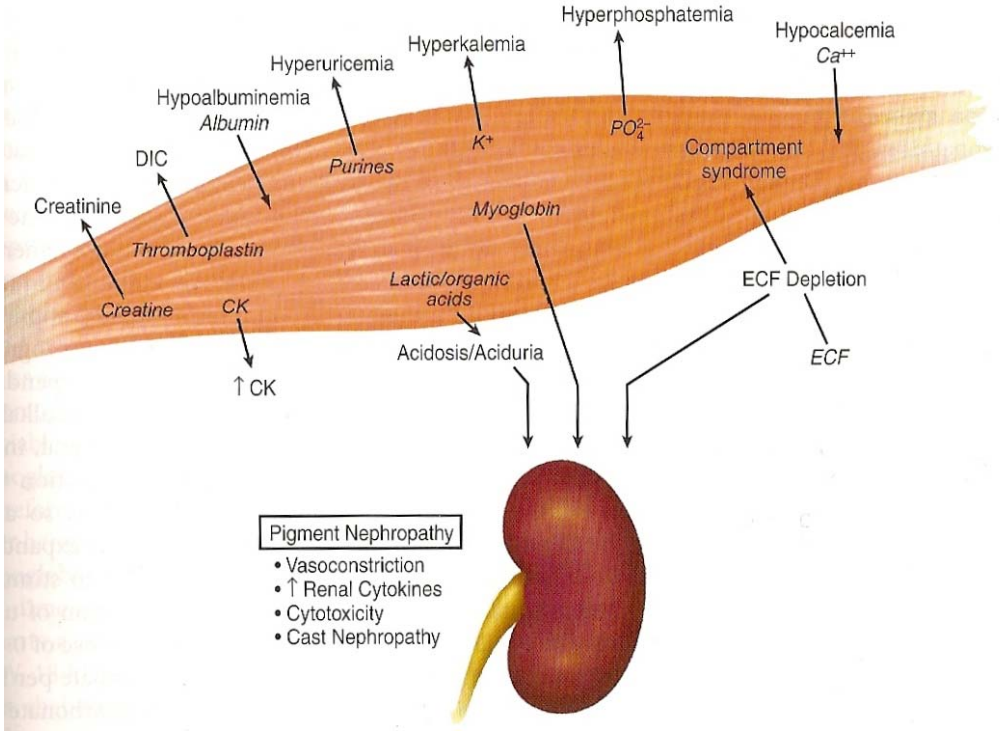
What *is* rhabdo?

A continuum…



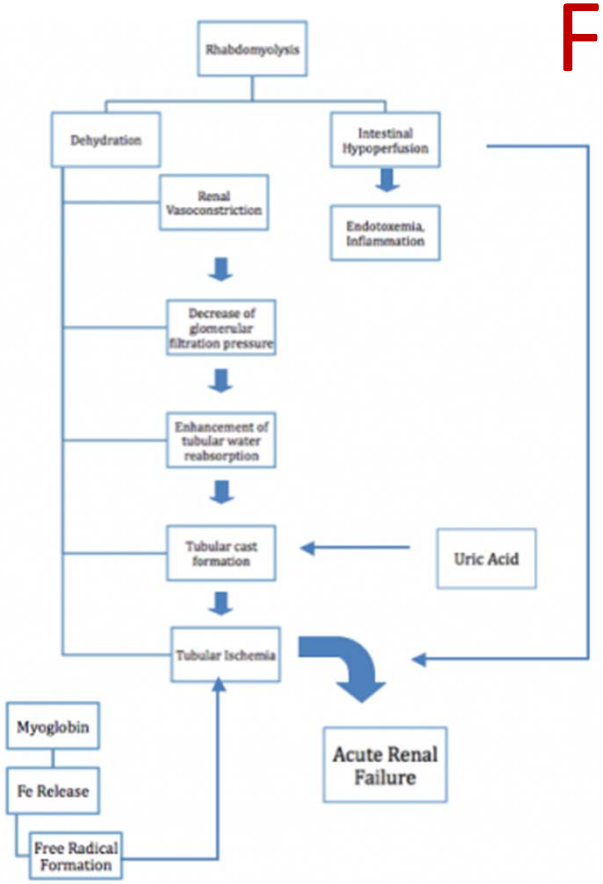
Muscles are not just your grandfather's bundles of actin/myosin

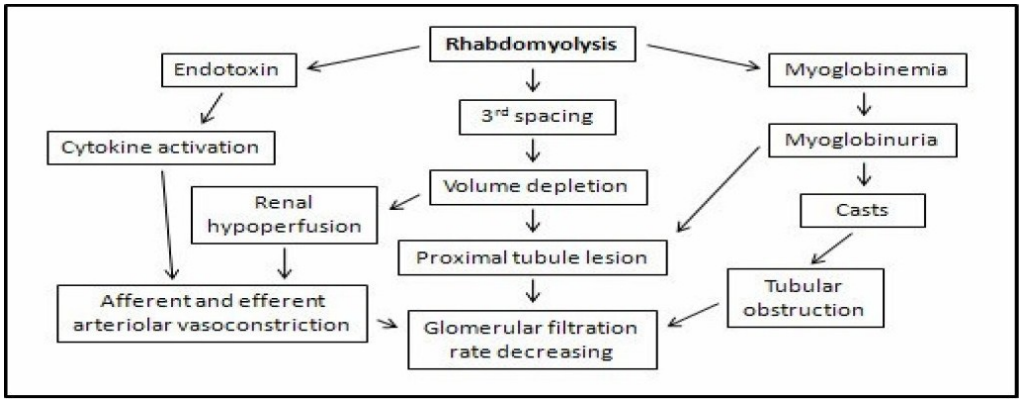




Lots of stuff that does bad things to the kidneys

For those who like physiology diagrams…





Common causes reported for rhabdo

Category	Commonly Reported Cause
Trauma	Crush syndrome
Exertion	Strenuous exercise, seizures, alcohol withdrawal syndrome
Muscle hypoxia	Limb compression by head or torso during prolonged immobilization or loss of consciousness,* major artery occlusion
Genetic defects	Disorders of glycolysis or glycogenolysis, including myophosphorylase (glycogenosis type V), phosphofructokinase (glycogenosis type VII), phosphorylase kinase (glycogenosis type VIII), phosphoglycerate kinase (glycogenosis type IX), phosphoglycerate mutase (glycogenosis type X), lactate dehydrogenase (glycogenosis type XI) Disorders of lipid metabolism, including carnitine palmitoyl transferase II, long-chain acyl-CoA dehydrogenase, short-chain L-3-hydroxyacyl-CoA dehydrogenase, medium-chain acyl-CoA dehydrogenase, very-long-chain acyl-CoA dehydrogenase, medium-chain 3-ketoacyl-CoA, thiolase† Mitochondrial disorders, including succinate dehydrogenase, cytochrome *c* oxidase, coenzyme Q10 Pentose phosphate pathway: glucose-6-phosphate dehydrogenase Purine nucleotide cycle: myoadenylate deaminase
Infections‡	Influenza A and B, coxsackievirus, Epstein–Barr virus, primary human immunodeficiency virus, legionella species *Streptococcus pyogenes, Staphylococcus aureus* (pyomyositis), clostridium
Body-temperature changes	Heat stroke, malignant hyperthermia, malignant neuroleptic syndrome, hypothermia
Metabolic and electrolyte disorders	Hypokalemia, hypophosphatemia, hypocalcemia, nonketotic hyperosmotic conditions, diabetic ketoacidosis
Drugs and toxins	Lipid-lowering drugs (fibrates, statins), alcohol, heroin, cocaine
Idiopathic (sometimes recurrent)	

Next slide

Drug causes

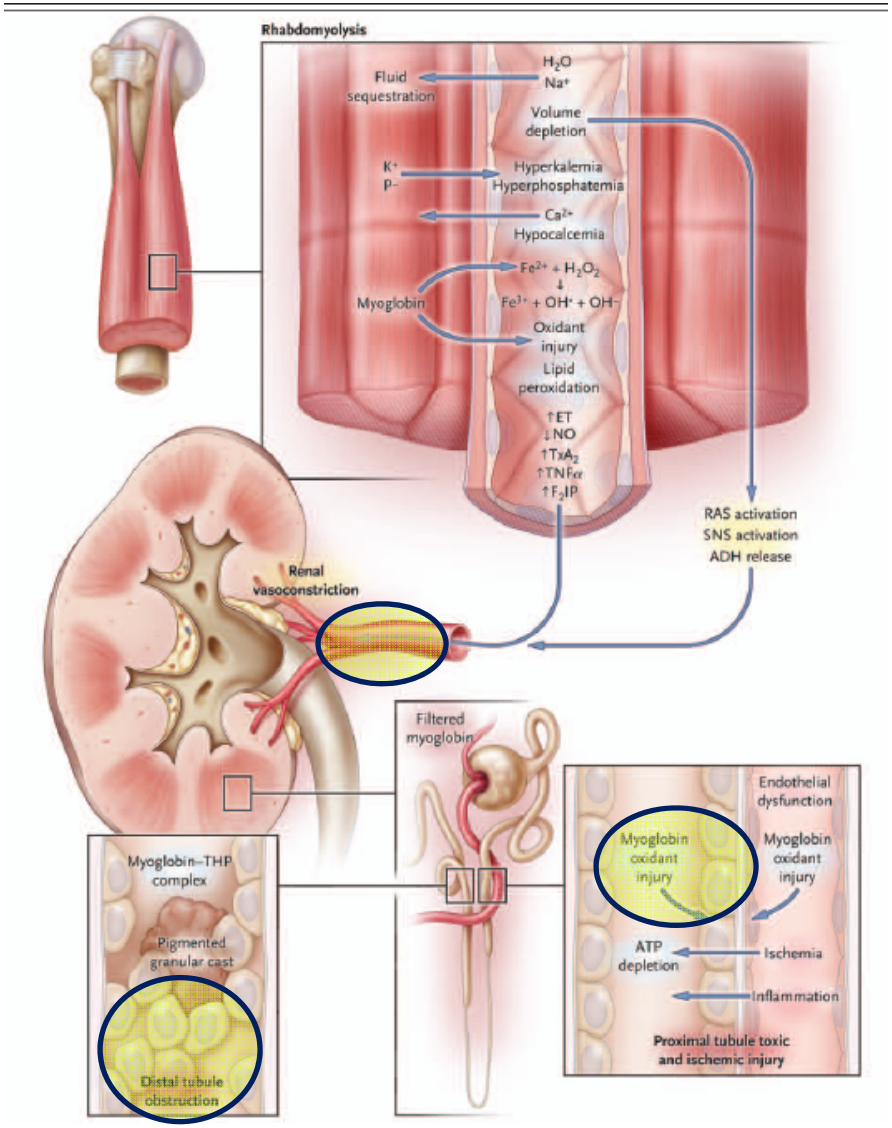
Drugs
Medications
Lipid-lowering agents
Statins
Fibrates
Psychiatric medications
Neuroleptics/antipsychotics (including haloperidol, atypical antipsychotics)
Selective serotonin reuptake inhibitors
Lithium
Valproic acid
Antimicrobial agents
Antiretroviral medications (protease inhibitors)
Trimethoprim-sulfamethoxazole
Daptomycin
Macrolide antibiotics
Quinolones
Amphotericin B
Anesthetics/paralytics
Succinylcholine
Propofol
Antihistamines
Doxylamine
Diphenhydramine
Appetite suppressants
Phentermine
Ephedra
Others
Sunitinib, erlotinib
Narcotics
Colchicine
Vasopressin
Amiodarone
Aminocaproic acid
Illicit drugs
Cocaine
Amphetamines/methamphetamines
Hallucinogens
Heroin
Methylenedioxypyrovalerone, mephedrone (bath salts)
Phencyclidine

Most common in int med practice

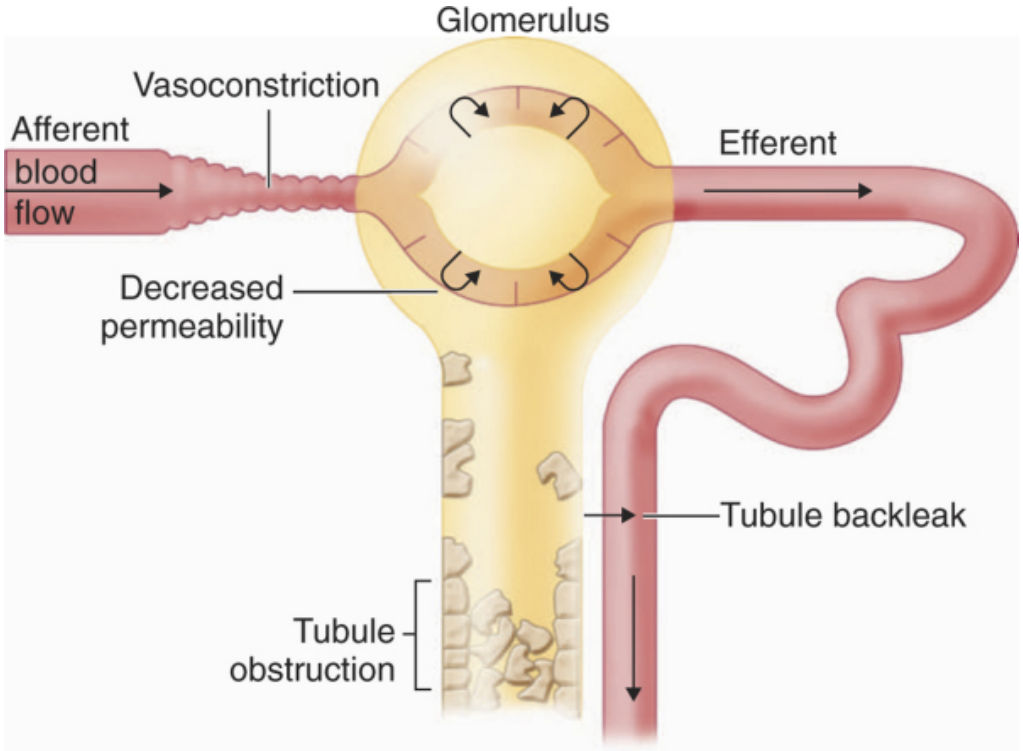
Probably most common at UCDMC (county hospital)

Pathogenesis of rhabdo

Renal lesions



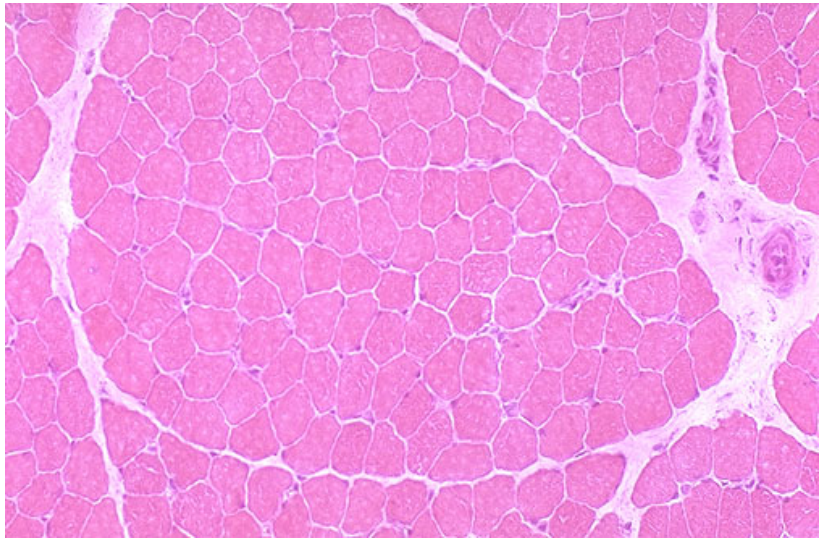
The <u>early</u> kidney lesion is *afferent arteriole vasoconstriction*



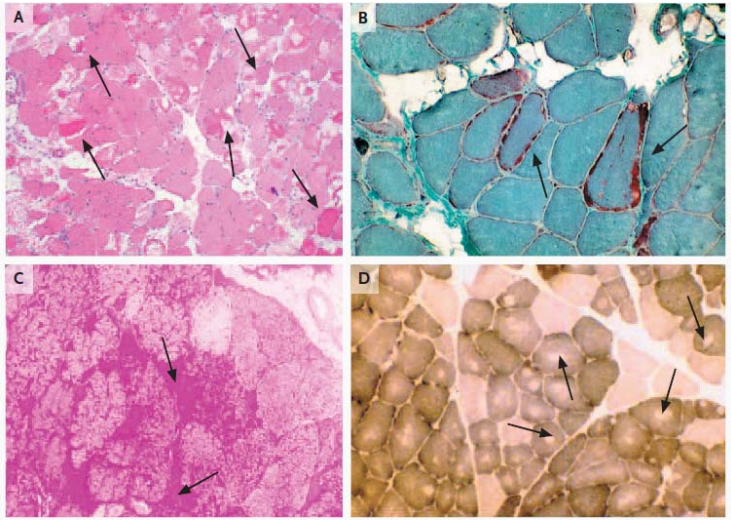
Appears “pre-renal” on urine chemistries (UNa <10 or FENa <1%) and is transient: within minutes/hours

Histopath: muscle injury

(no surprise)

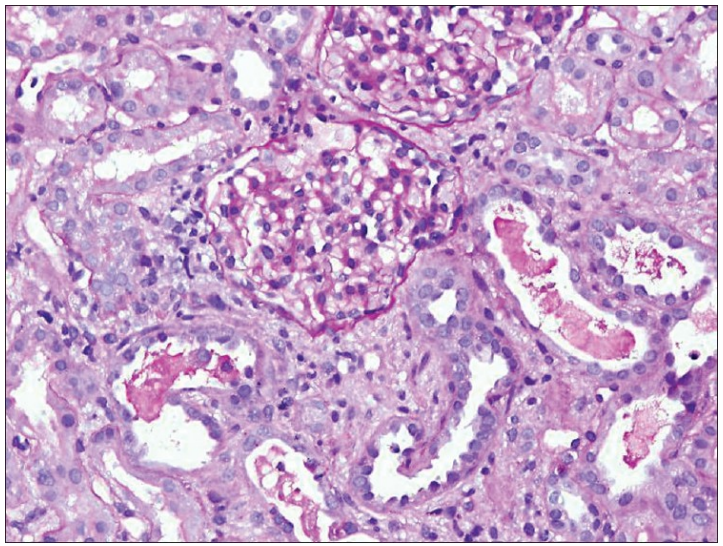


normal

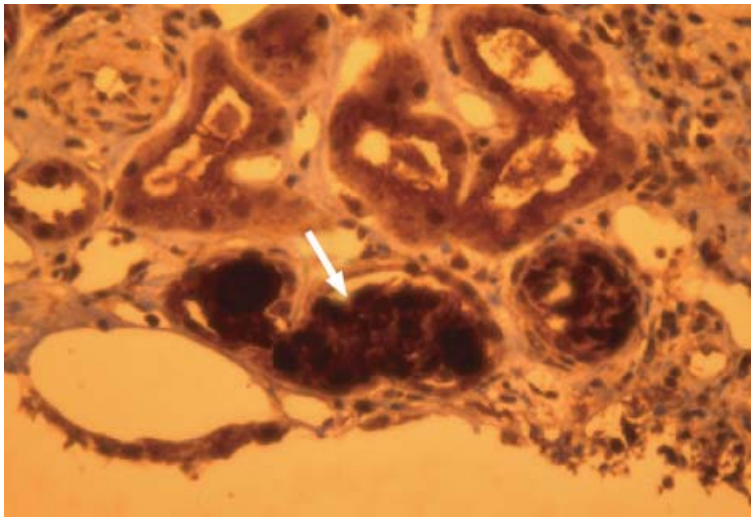


Various rhabdo cases

Histopath: kidney



ATN (ischemia)



Myoglobin precipitates *only with* Tamm-Horsefall protein; worse (in vitro) in acid urine

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Diagnosis of Rhabdo

- Need to think about it! (high index of suspicion): for example during an ultramarathon in the heat.
- Ask about muscle symptoms (pain, cramps) and signs: look for signs of crush injury or evidence of extreme exertion (i.e. 100 mile run in the heat)
- Ask about drugs (i.e. statins, lithium, cocaine, heroin)
- Ask about color of urine

Diagnosis of Rhabdo:

urinary findings

Color	Dark (cola-colored)
pH	Acidic
Blood	
Benzidine reagent	3+ to 4+
Microscopy	Less than 5 RBCs per high powered field
Sediment	Pigmented brown granular casts Renal tubular epithelial cells
Urinary Sodium Concentration	>20 mEq/L
FE_{NA} (functional excretion of sodium)	> 1%

Key *medical student* finding on UA: heme (++) but *no* RBCs

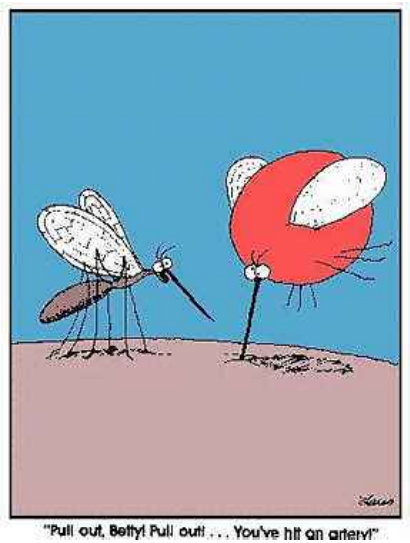
Differential dx of red and brown urine

Cause	Results of Test for Blood in Fresh Urine*	Sediment†‡	Supernatant‡
Hematuria	+ to ++++	Red	Yellow
Myoglobinuria	+ to ++++	Normal	Red to brown
Hemoglobinuria	+ to ++++	Normal	Red to brown
Porphyria	Negative	Normal	Red
Bile pigments	Negative	Normal	Brown
Food and drugs§	Negative	Normal	Red to brown

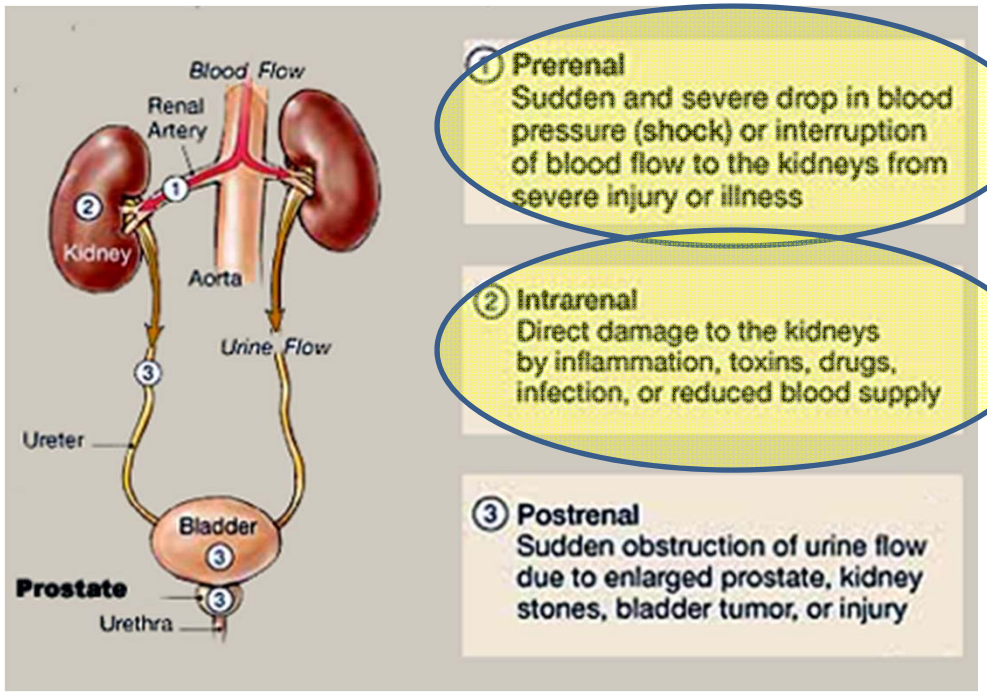
Initial laboratory findings in rhabdo

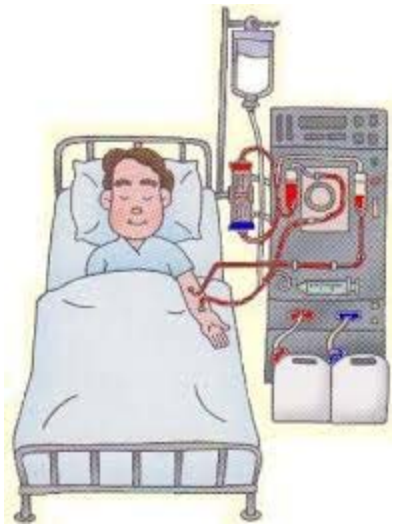
Test	Abnormal Value for Rhabdomyolysis	Comments
CK	>500 IU/L	Diagnostic for rhabdomyolysis; increased risk of kidney injury if >5,000 IU/L
Potassium	>6.0 mmol/L	Marker of severity of muscle injury and renal dysfunction
	<2.0 mmol/L	Potential cause of rhabdomyolysis
Phosphorous	>6.0 mg/dL	Marker of severity of muscle injury and renal dysfunction
	<2.0 mg/dL	Potential cause of rhabdomyolysis
Calcium	Decreased (<8.0 mg/dL)	Deposition in damaged muscle
Creatinine	Increased	Marker of decreased renal function
BUN:creatinine	<10:1, often <6:1	Increased conversion of muscle creatine to creatinine
Anion gap	Increased	Increased organic acids due to muscle injury or renal dysfunction
Blood alcohol level	Elevated	Potential cause of rhabdomyolysis
Urine blood dipstick	Positive	Detects myoglobinuria in absence of RBCs in urine
Urine drug screen	Positive	Potential drug-related cause of rhabdomyolysis

BUN = blood urea nitrogen; CK = creatine kinase.



Late laboratory findings





Seen in rhabdo

Too late…

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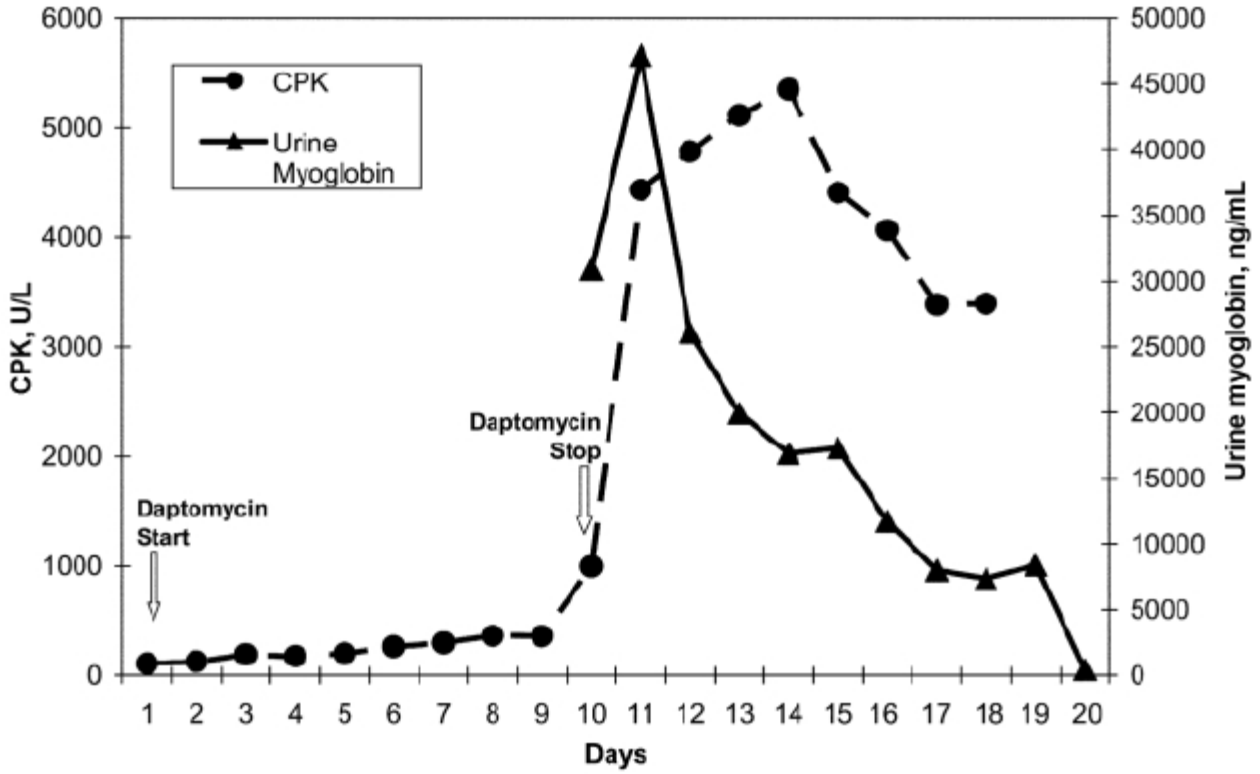
Course of rhabdo

- Depends on severity of insult, duration, ambient temperature, hydration status
- *Issue of hyponatremia vs. sufficient fluid to prevent/treat rhabdo*

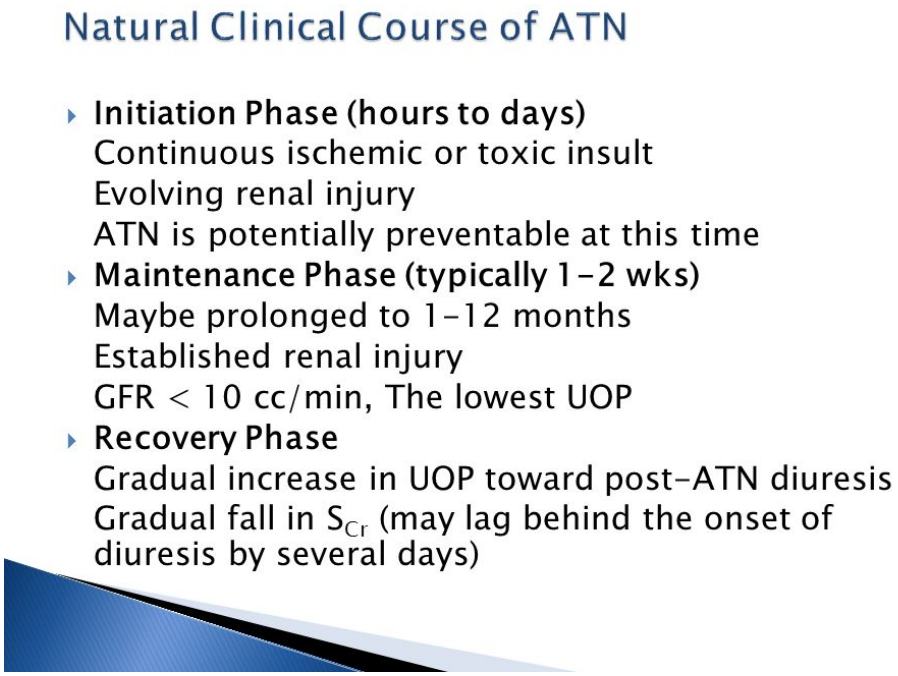
Example: Course of daptomycin-induced rhabdo

(only example I could find)



If AKI intervenes…

- A triple whammy
  - Pre-renal vasoconstriction
  - Intra-renal cast formation
  - Tubular toxicity



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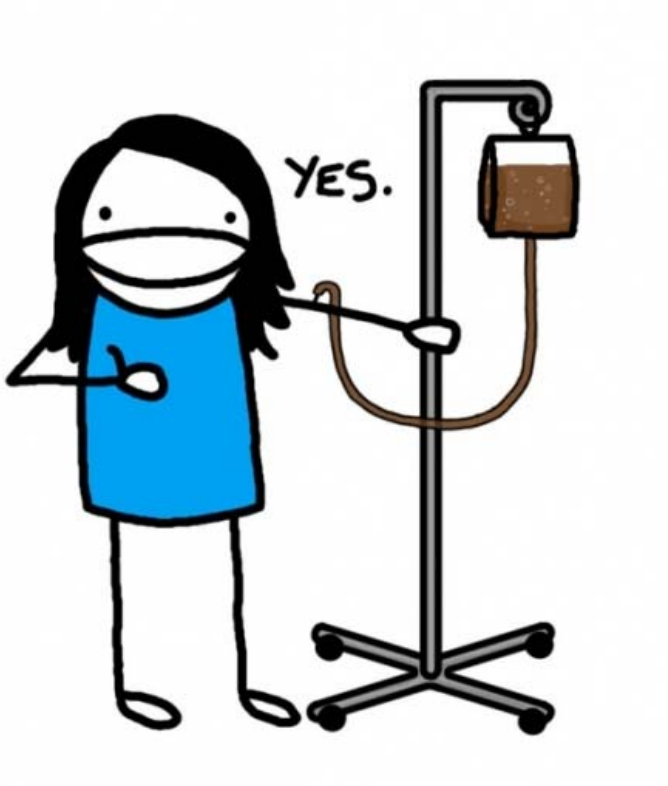
Treatment is very controversial because…

- No controlled trials of saline-based fluid vs. bicarbonate (hard to believe…)
  - Lamenting this since I was a nephrology fellow in the 80's
- Bicarbonate recommendations based on lab (chemical) and animal studies only
- Overshoot alkalosis with bicarb can *worsen hypocalcemia*
- Many physicians (especially ER docs!) have their favorite recipes frequently not based on science
- Consensus: *give fluids!*



Treatment: a recipe

Check for extracellular volume status, central venous pressure, and urine output.*

Measure serum creatine kinase levels. Measurement of other muscle enzymes (myoglobin, aldolase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) adds little information relevant to the diagnosis or management.

Measure levels of plasma and urine creatinine, potassium and sodium, blood urea nitrogen, total and ionized calcium, magnesium, phosphorus, and uric acid and albumin; evaluate acid–base status, blood-cell count, and coagulation.

Perform a urine dipstick test and examine the urine sediment.

Initiate volume repletion with normal saline promptly at a rate of approximately 400 ml per hour (200 to 1000 ml per hour depending on the setting and severity), with monitoring of the clinical course or of central venous pressure.

Target urine output of approximately 3 ml per kilogram of body weight per hour (200 ml per hour).

Check serum potassium level frequently.

Correct hypocalcemia only if symptomatic (e.g., tetany or seizures) or if severe hyperkalemia occurs.

Investigate the cause of rhabdomyolysis.

Check urine pH. If it is less than 6.5, alternate each liter of normal saline with 1 liter of 5% dextrose plus 100 mmol of bicarbonate. Avoid potassium and lactate-containing solutions.

Consider treatment with mannitol (up to 200 g per day and cumulative dose up to 800 g). Check for plasma osmolality and plasma osmolal gap. Discontinue if diuresis (>20 ml per hour) is not established.

Maintain volume repletion until myoglobinuria is cleared (as evidenced by clear urine or a urine dipstick testing result that is negative for blood).

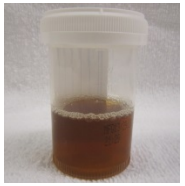
Consider renal-replacement therapy if there is resistant hyperkalemia of more than 6.5 mmol per liter that is symptomatic (as assessed by electrocardiography), rapidly rising serum potassium, oliguria (<0.5 ml of urine per kilogram per hour for 12 hours), anuria, volume overload, or resistant metabolic acidosis (pH <7.1).

* In the case of the crush syndrome (e.g., earthquake, building collapse), institute aggressive volume repletion promptly before evacuating the patient.

NEJM 2009

Treatment summary

- In the field:
  - muscle pain and/or dark urine: check volume status
  - Normal saline (or HTS) hydration, being cognizant of the possibility of EAH
  - *Consider* bicarbonate
  - Avoid sports drinks (K+)
  - Recommend hospitalization



Complications of Rhabdo

Hypovolaemia
Compartment syndrome
Arrhythmias and cardiac arrest
Disseminated intravascular coagulation
Hepatic dysfunction
Acidosis
Acute renal failure

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WSER 2009

Table 1. Initial biochemical values (and range of values during treatment) in all 5 hospitalized cases of hyponatremia with rhabdomyolysis competing in the 2009 Western States Endurance Run

Case No.	*Blood [Na^+] mmol/L (range)*	*Blood [K^+] mmol/L (range)*	*Blood BUN mg/dL (range)*	*Blood Creatinine mg/dL (range)*	*Blood CPK U/L (range)*	*Urinalysis*	*Days in hospital*	*Developed acute renal failure*
1	134 (128–135)	4.9 (3.5–4.9)	54 (54–113)	3.1 (3.1–10.3)	>40 000 (9029–785 250)	+3 blood +protein	12	Yes
2	129 (129–142)	3.4 (3.4–3.9)	69 (33–69)	4.9 (2.0–4.9)	38 218 (6078–38 218)	+3 blood trace protein	3	Yes
3	127 (127–139)	3.6 (3.6–4.2)	23 (14–23)	1.2 (1.0–1.2)	95 940 (35 912–95 940)	+4 blood +1 protein	<2	No
4	131 (131–143)	4.4 (4.1–4.8)	43 (39–46)	2.8 (2.7–3.2)	>40 000 (19 534–>40 000)	+1 blood 0 protein	1	Yes
5	131 (131–140)	3.9 (3.6–3.9)	18 (10–18)	1.1 (1.1–1.2)	40 095 (17 950–40 095)	+4 blood +2 protein	1	No

Bruso, Hoffman et al, 2010

Who progressed to AKI and who didn't

Table 2. Demographics, training history, symptoms, weight change, and biochemical values in hospitalized cases of hyponatremia with rhabdomyolysis who did (n = 3) and did not (n = 2) progress to acute renal failure after the 2009 Western States Endurance Run

Variable	*Progressing to acute renal failure*	*Not progressing to acute renal failure*
Age (years)	36.7 ± 7.8	42.0 ± 7.1
Finish time (hours)	24.3 ± 4.6	Did not finish
Prior 161–km ultramarathon finishes (no.)	5.3 ± 6.8	2.5 ± 3.5
Change in body weight (%)	−1.3 ± 3.8	2.5 ± 3.5
Initial blood [Na^+] (mmol/L)	131.3 ± 2.5	129.0 ± 2.8
Initial blood [K^+] (mmol/L)	4.2 ± 0.8	3.8 ± 0.2
Initial blood CPK (U/L)	38 218–>40 000	40 095–95 940
Initial blood BUN (mg/dL)	43–69	18–23
Initial blood creatinine (mg/dL)	2.8–4.9	1.1–1.2
Presence of nausea (% of cohort)	67	50
Injury interfering with training (% of cohort)	100	50

Data are presented as mean ± SD, range or percentage.

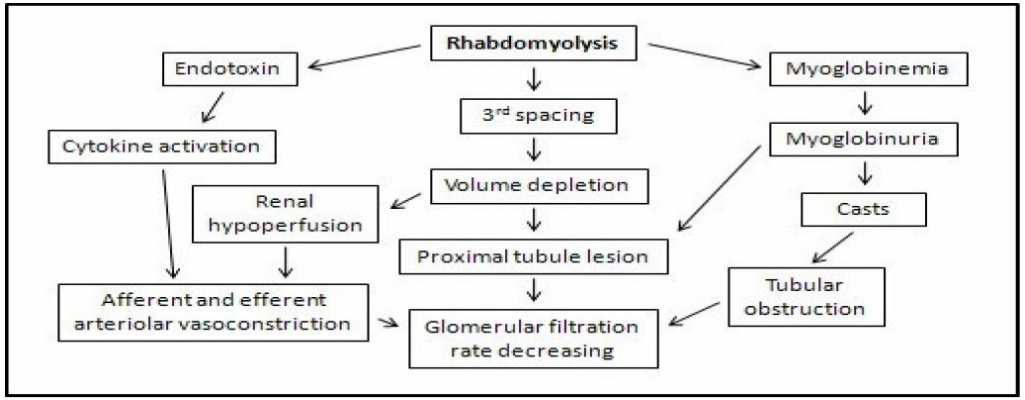
When to return after a rhabdo episode

Table 2. CHAMP guidelines for return to sport following exertional rhabdomyolysis

Phase 1 • Rest for 72 hours and encouragement of oral hydration • 8 hours of sleep nightly • Remain in a thermally controlled environment if the episode of ER was in relation to heat illness • Follow-up after 72 hours with a repeat serum CK level and UA • If the CK has dropped to below 5 times the upper limit of normal and the UA is negative, the athlete can progress to phase 2; if not, reassessment in 72 additional hours is warranted • Should the UA remain abnormal or the CK remain elevated for 2 weeks, expert consultation is recommended
Phase 2 • Begin light activities, no strenuous activity • Physical activity at own pace/distance • Follow-up with a care provider in 1 week • If there is no return of clinical symptoms, the athlete can progress to phase 3; if not, the athlete should remain in phase 2 checking with the health care professional every week for reassessment; if muscle pain persists beyond the fourth week, consider expert evaluation to include psychiatry
Phase 3 • Gradual return to regular sport/physical training • Follow-up with care provider as needed

CHAMP, Consortium for Health and Military Performance; ER, exertional rhabdomyolysis; CK, creatine kinase; UA, urinalysis.

Horses get it too

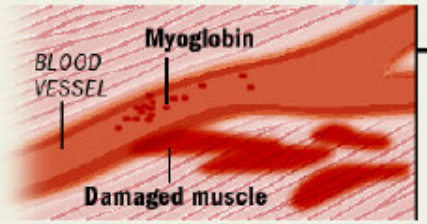

Rhabdomyolysis
Endotoxin
Myoglobinemia
3rd spacing
Cytokine activation
Myoglobinuria
Volume depletion
Renal hypoperfusion
Casts
Proximal tubule lesion
Tubular obstruction
Afferent and efferent arteriolar vasoconstriction
Glomerular filtration rate decreasing

Bad blood

Rhabdomyolysis can be caused by injuries or conditions that damage skeletal muscle. Heat stroke, severe exertion or trauma can increase the risk.

BROKEN DOWN

Muscle-fiber contents known as myoglobin are released into the bloodstream when damaged muscle tissue ruptures.



SIDE EFFECTS

KIDNEY DAMAGE

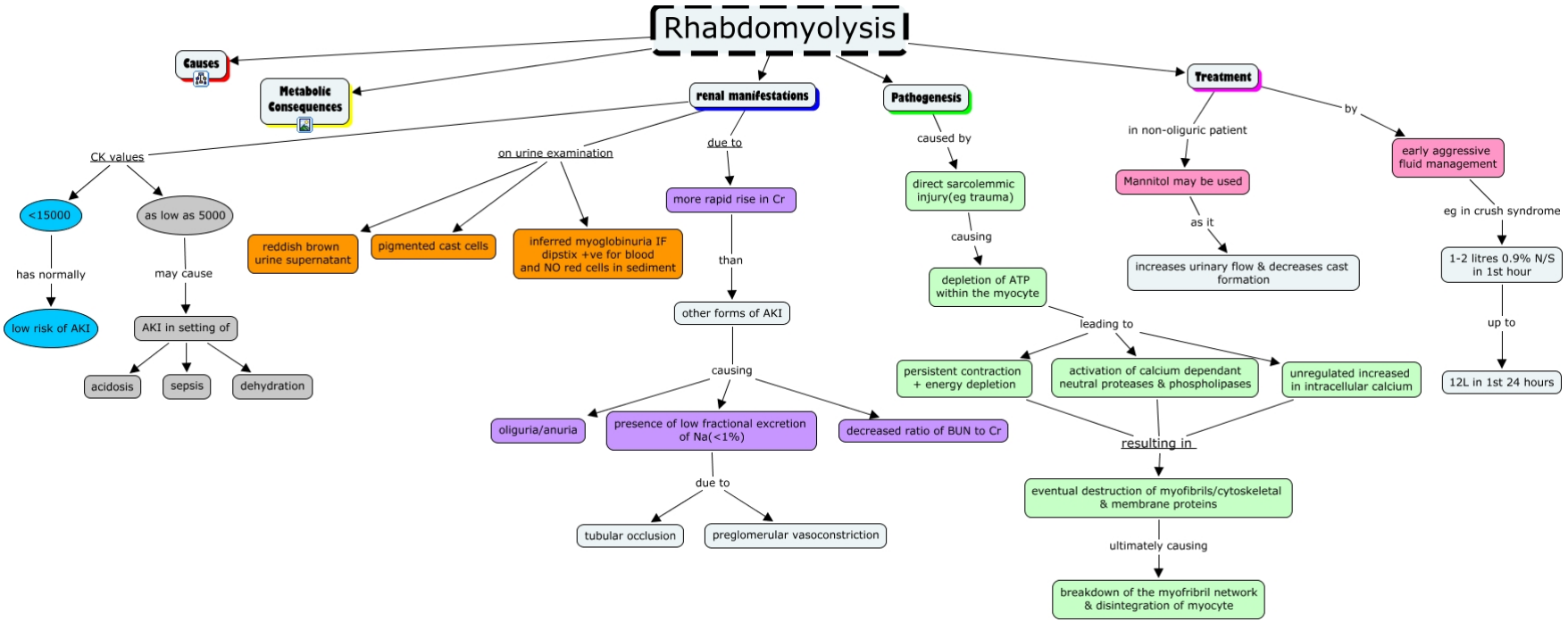
Myoglobin is filtered out of the body through the kidneys but breaks down into substances that can cause renal injuries.

DARK URINE

Urine of an abnormal color (red or dark brown) can indicate kidney damage.

Source: U.S. National Library of Medicine

THE COLUMBUS DISPATCH


Rhabdomyolysis
Causes
Metabolic Consequences
renal manifestations
Pathogenesis
Treatment
CK values
<15000
as low as 5000
has normally
low risk of AKI
may cause
AKI in setting of
acidosis
sepsis
dehydration
on urine examination
reddish brown urine supernatant
pigmented cast cells
inferred myoglobinuria IF dipstix +ve for blood and NO red cells in sediment
due to
more rapid rise in Cr
than
other forms of AKI
causing
oliguria/anuria
presence of low fractional excretion of Na(<1%)
decreased ratio of BUN to Cr
due to
tubular occlusion
preglomerular vasoconstriction
caused by
direct sarcolemmic injury(eg trauma)
causing
depletion of ATP within the myocyte
leading to
persistent contraction + energy depletion
activation of calcium dependant neutral proteases & phospholipases
unregulated increased in intracellular calcium
resulting in
eventual destruction of myofibrils/cytoskeletal & membrane proteins
ultimately causing
breakdown of the myofribril network & disintegration of myocyte
in non-oliguric patient
Mannitol may be used
as it
increases urinary flow & decreases cast formation
by
early aggressive fluid management
eg in crush syndrome
1-2 litres 0.9% N/S in 1st hour
up to
12L in 1st 24 hours