Dehydration and Kidney Injury: a Real Concern?

Causes of AKI during an ultra

(including new Knowledge from WSER Research)

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Outline of talk

- Case presentations
- Causes of renal failure (AKI) in an ultramarathon
- Most *serious*: rhabdomyolysis
- Most *common*: dehydration
- Most *dumb*: NSAIDs
- From WSER research: Does AKI from ultramarathons put you at risk for successive AKI?

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 .

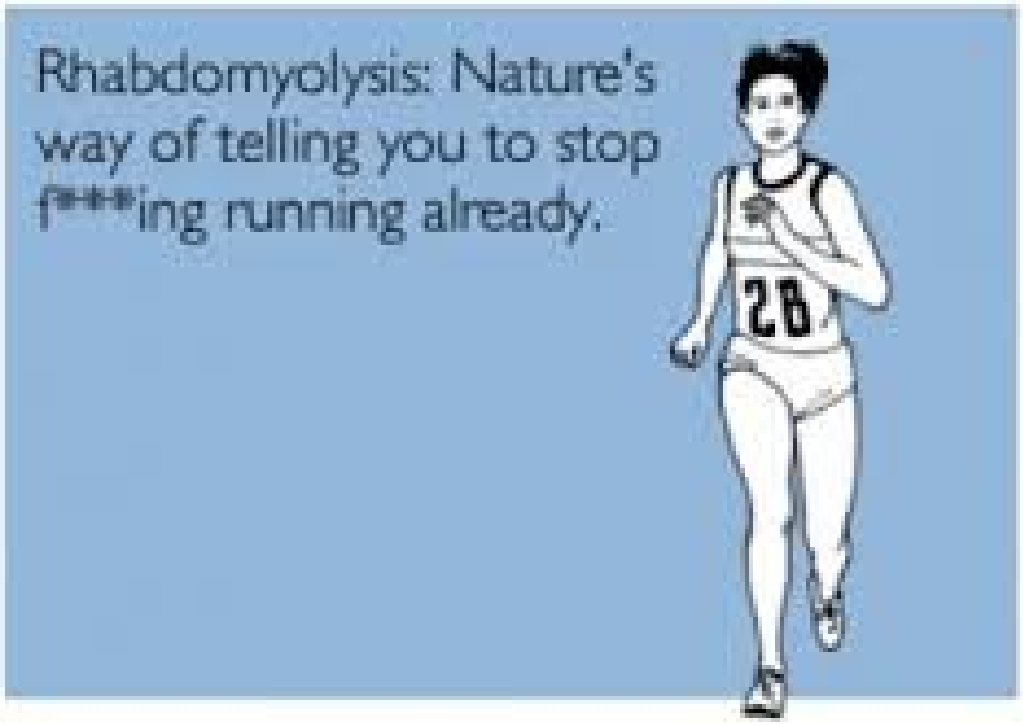
• **Case #2:** A 40-year old AA male developed rhabdomyolysis in his biceps after doing several sets of "negative curls". These are exercises where a spotter helps lift a heavy barbell up (concentric phase), and then the weight-lifter lowers the barbell (without assistance) until his arms are in an extended 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).

• **Case #3:** A 21-year old ultrarunner without previous medical history had serious muscle cramps in the middle of a marathon race when the temperature was 98^{o}F and so she took an 800 mg ibuprofen. Subsequently, she had blood drawn when she went to her PMD later that day feeling tired (duh!) and on screening blood tests her creatinine was 2.2 mg/dl (normal ~0.8). The fractional excretion of sodium in the urine was 0.5%. Blood chemistries a week later were normal.

Causes of AKI during (ultra)marathons

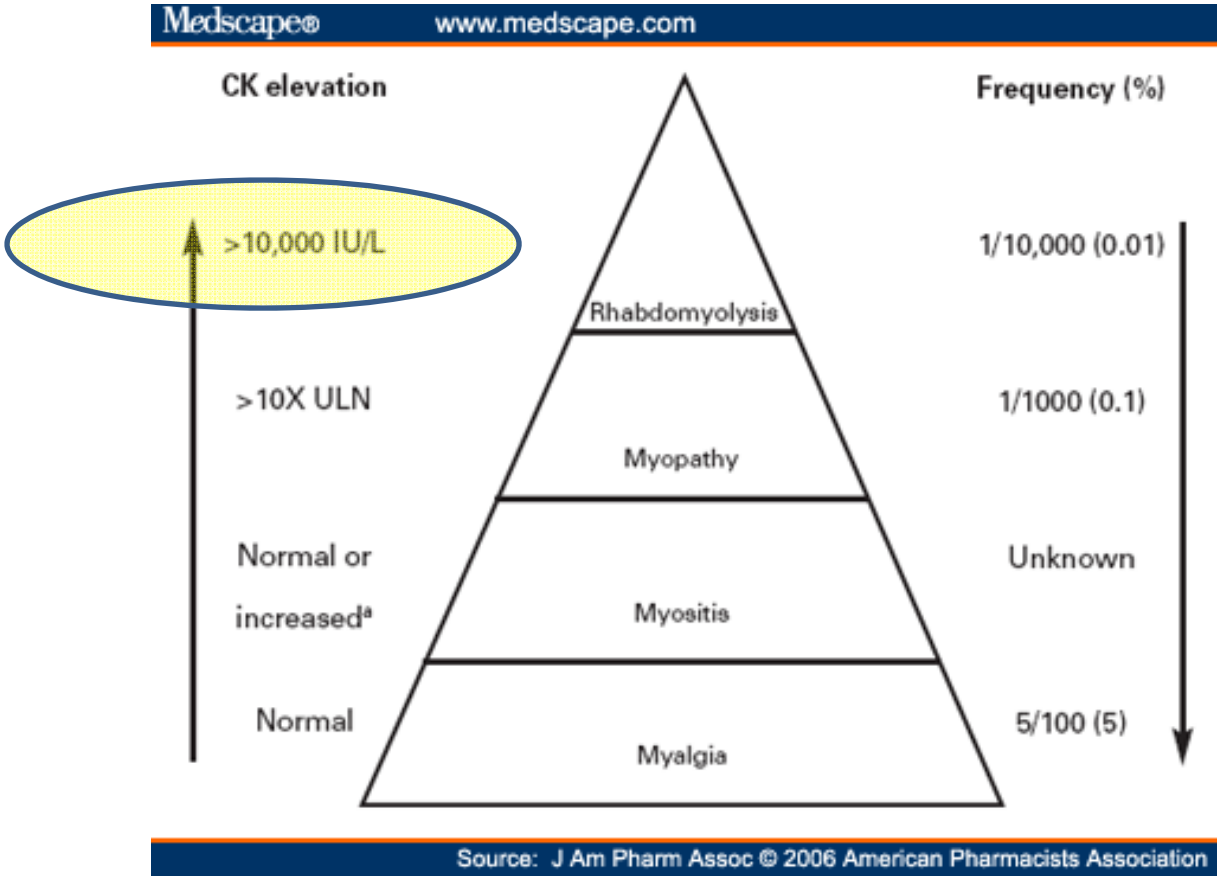
- Ranges from 38-80% following ultramarathons
- Many of these are essentially lab abnormalities and do *not* indicated renal damage (i.e. acute tubular necrosis, ATN)
- Most cases of lab abnormalities are “pre-renal”
  - Volume depletion→decreased effecive arterial volume
  - Exacerbation by NSAIDs (hemodynamic)
  - Some have postulated cardiac “exhaustion” leading to *cardiorenal syndrome* but that has to be rare in the ultra population
- Most common cause of <u>ATN</u> is rhabdomyolysis

Most nasty kind of AKI

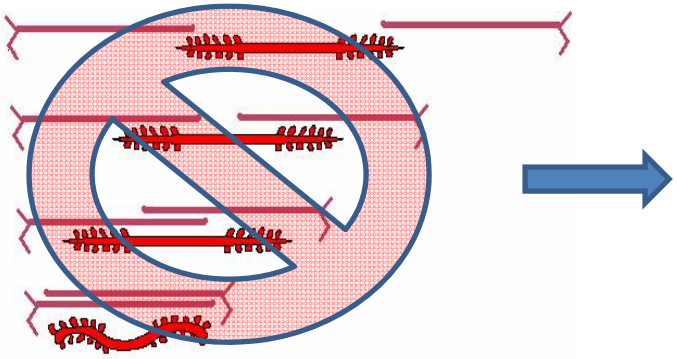


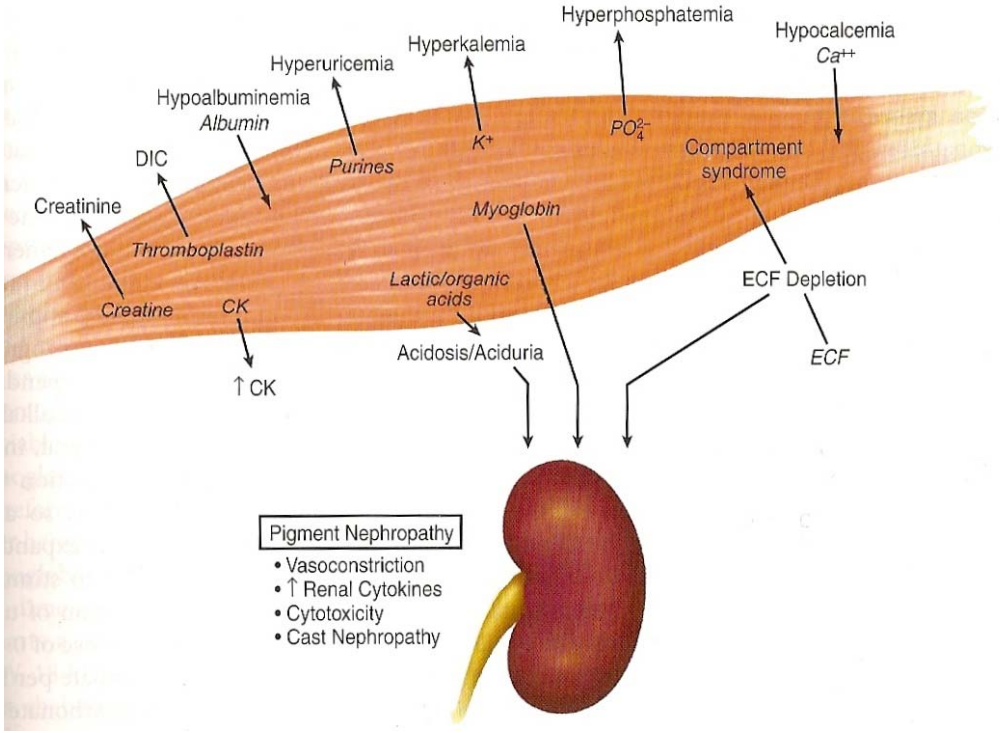
What *is* rhabdo?

A continuum…



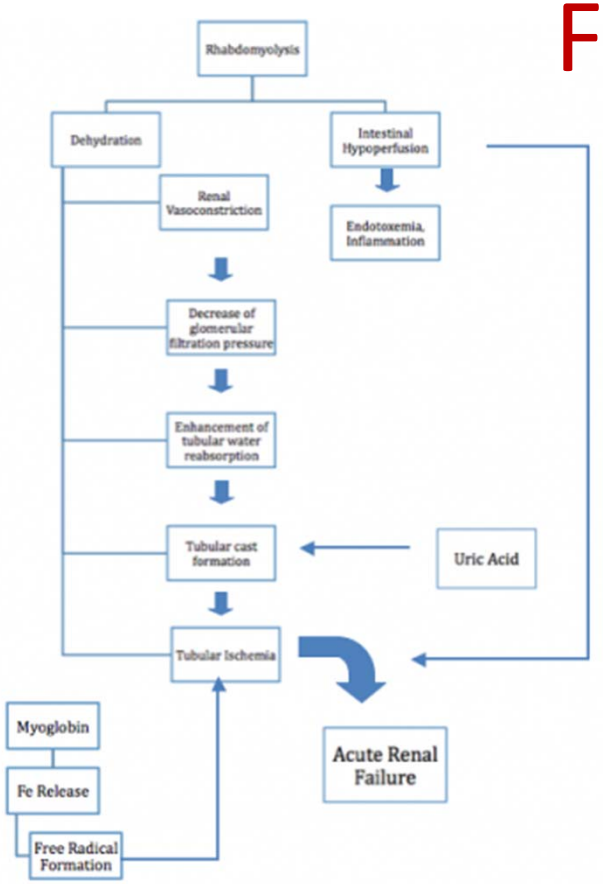
Muscles are not just your grandfather's bundles of actin/myosin

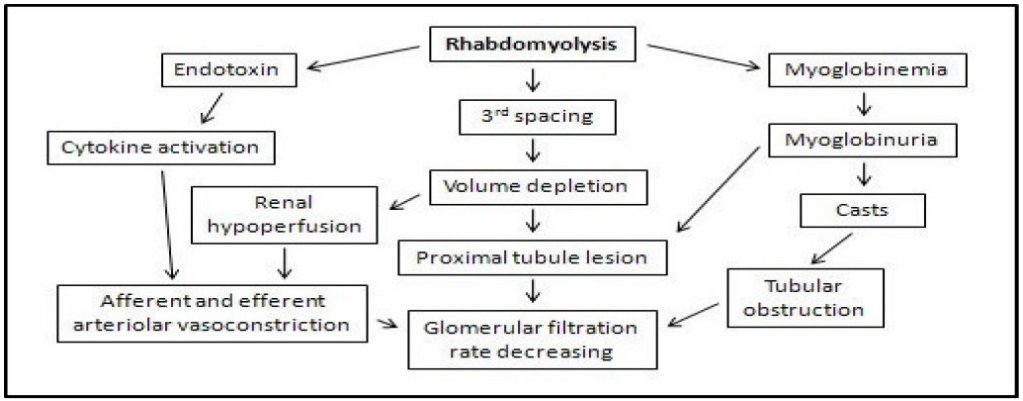




Lots of stuff that does bad things to the kidneys

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

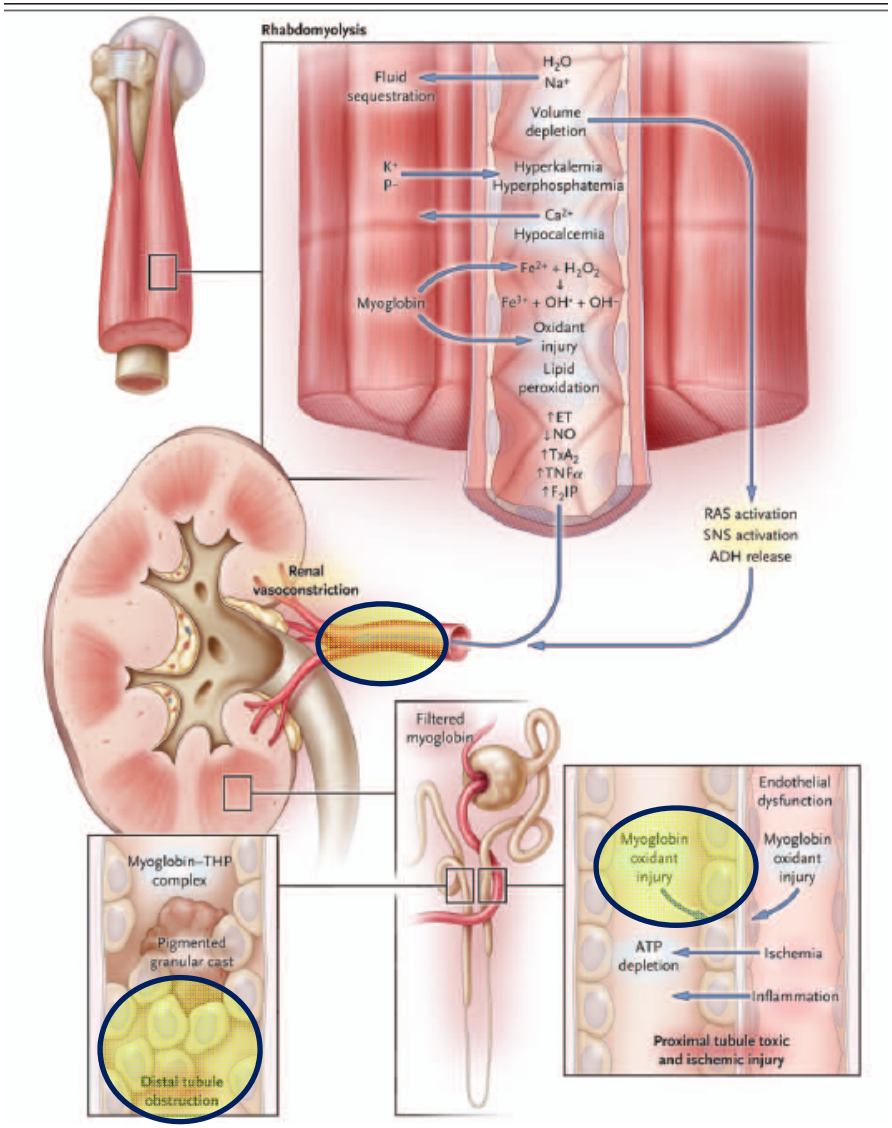
Drugs
Medications
Lipid-lowering agents
Statins
Fibrates
Psychiatric medications
Neuroleptics/antipsychotics (including haloperidol, atypical antipsychotics)
Selective serotonin reuptake inhibitors
Lithium
Valproic acid
Antimicrobial agents
Antiretroviral medications (protease inhibitors)
Trimethoprim-sulfamethoxazole
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



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

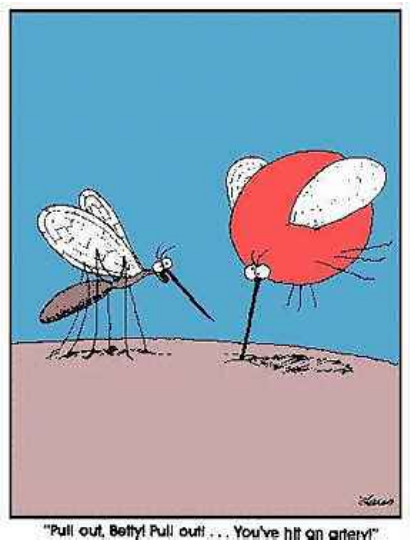
Color	Dark (cola-colored)
pH	Acidic
Blood	
Benzidine reagent	3+ to 4+
Microscopy	Less than 5 RBCs per high powered field
Sediment	Pigmented brown granular casts Renal tubular epithelial cells
Urinary Sodium Concentration	>20 mEq/L
FE_{NA} (functional excretion of sodium)	> 1%

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

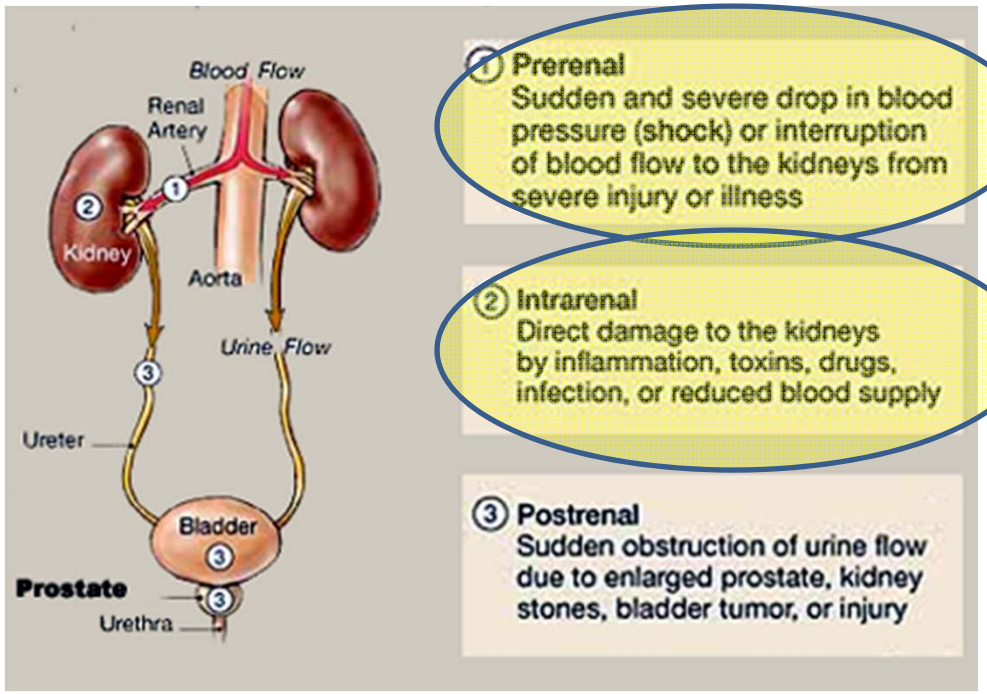
Initial laboratory findings in rhabdo

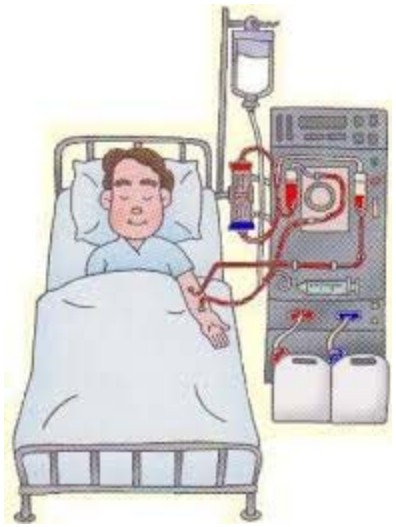
Test	Abnormal Value for Rhabdomyolysis	Comments
CK	>500 IU/L	Diagnostic for rhabdomyolysis; increased risk of kidney injury if >5,000 IU/L
Potassium	>6.0 mmol/L	Marker of severity of muscle injury and renal dysfunction
	<2.0 mmol/L	Potential cause of rhabdomyolysis
Phosphorous	>6.0 mg/dL	Marker of severity 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



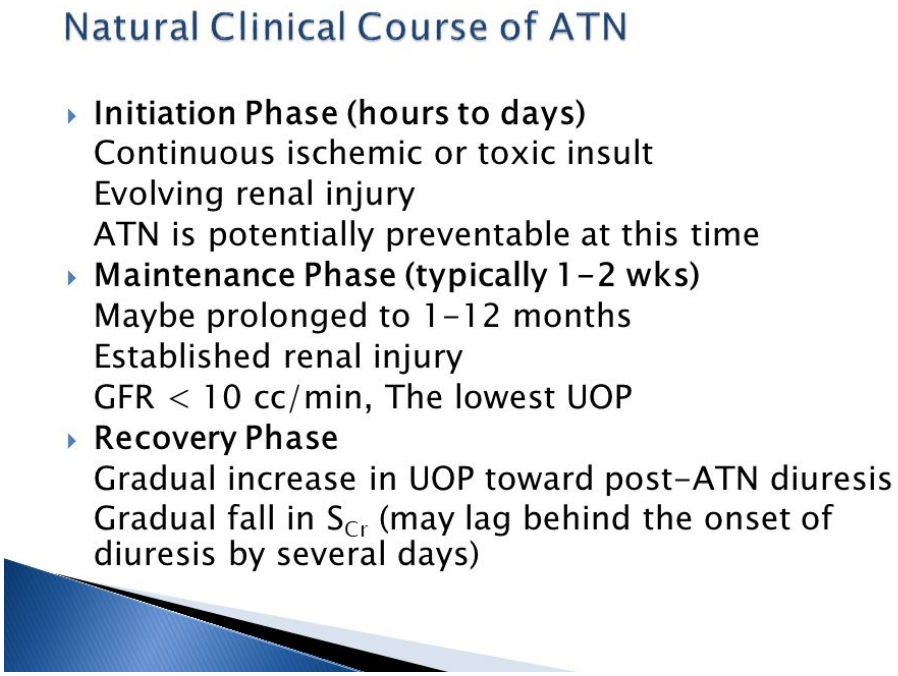


Seen in rhabdo

Too late…

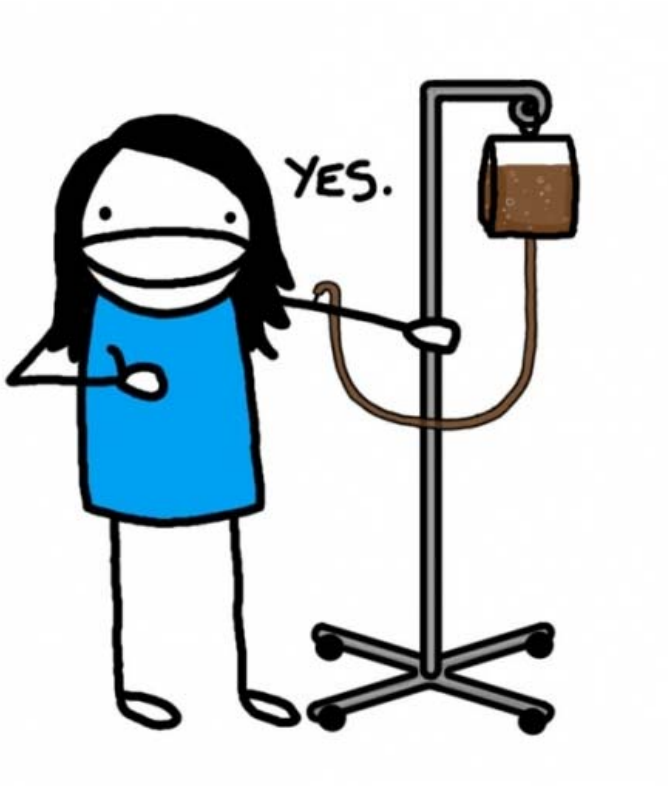
If AKI intervenes…

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



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.

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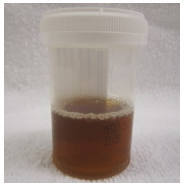
Treatment summary

- 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



When to return after a rhabdo episode

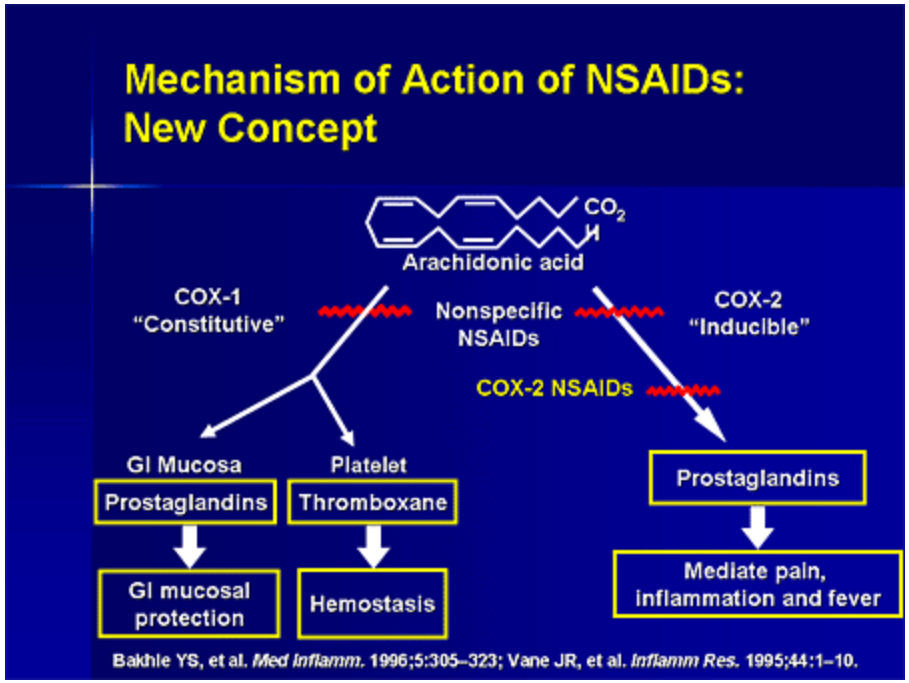
Table 2. CHAMP guidelines for return to sport following exertional rhabdomyolysis

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.

NSAID-induced AKI

- Very commonly used pain/inflammatory medicine
- Mechanism: inhibition of a variety of pathways including vasodilatory prostaglandins→
- attenuation of afferent vasodilation
- Can lead to ATN especially with volume depletion



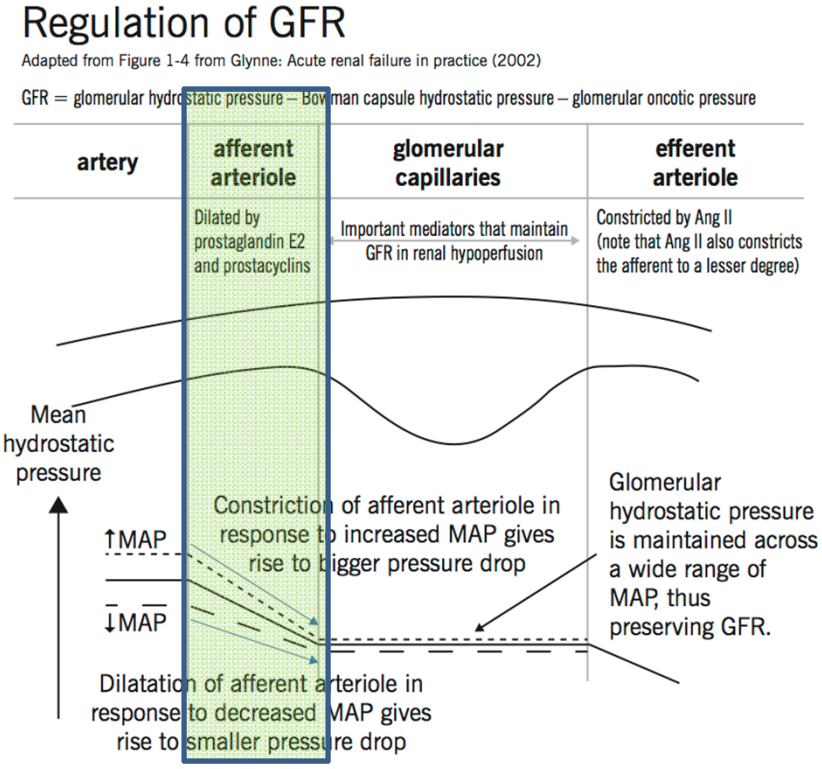
NSAID-induced AKI

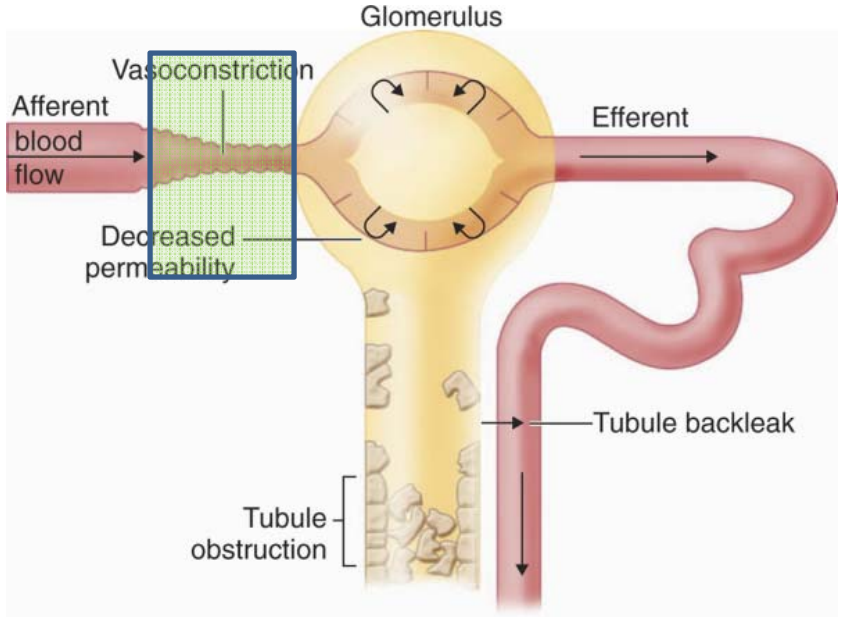
most dumb, most preventable, most dumb, most stupid

NSAID-induced AKI:

why are these drugs so nasty?

Because they affect prostaglandins which are vaso-active

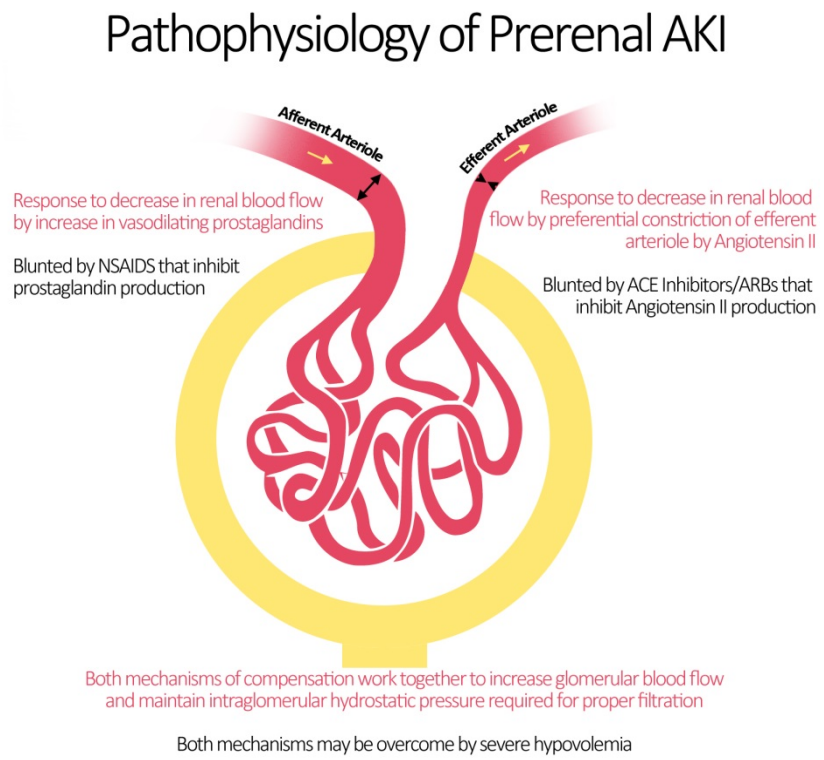




Appears “pre-renal” on urine chemistries (UNa <10 or FENa <1%) and is transient: within minutes/hours

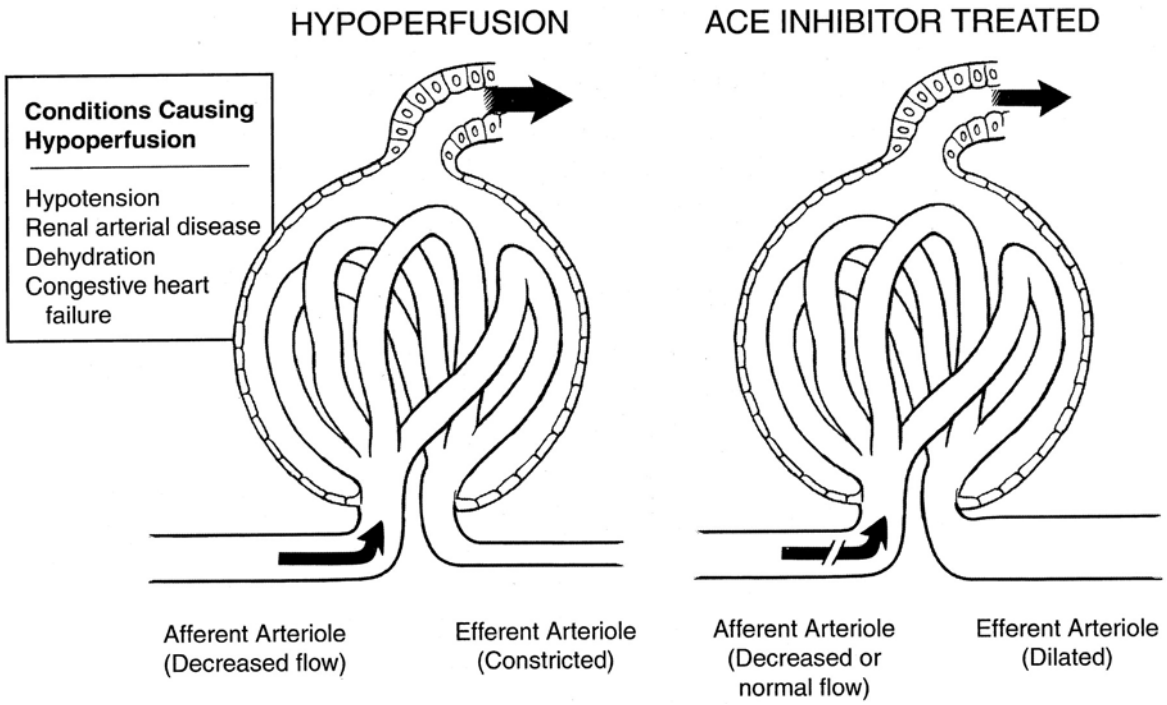
Here's what we see in clinic: NSAID plus ACEI/ARB are a very bad combination

due to action on both incoming and outgoing arterioles

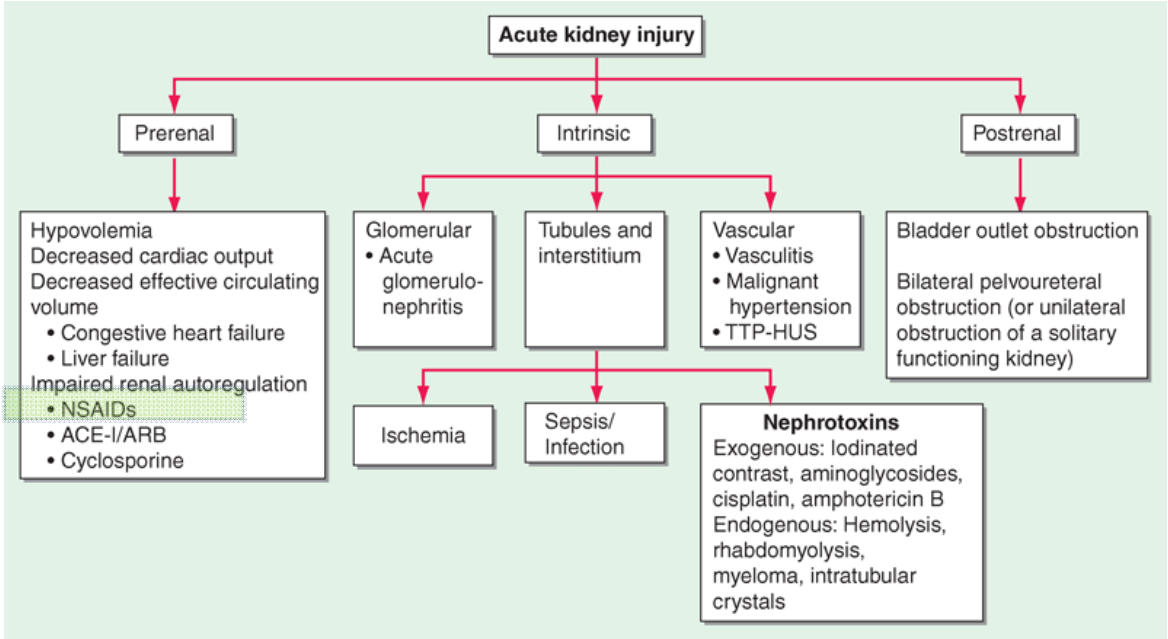


If you are dehydrated, the NSAIDs are even worse

same withcardiorenal



Diagnosis of NSAID-induced AKI



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

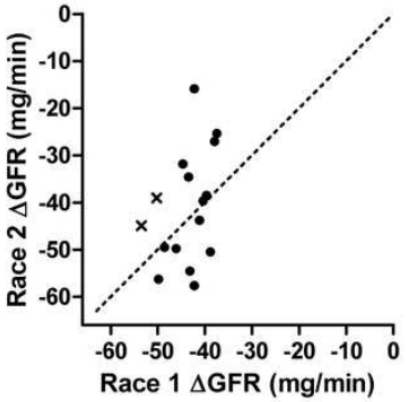
Low UNa, low FENa, high BUN/Creatinine ratio

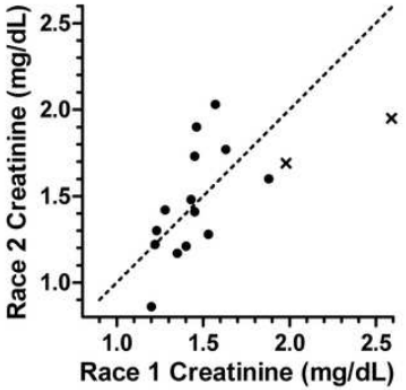
Treatment of NSAID-induced AKI

- Stop NSAID (duh)
- Same as volume depletion: *give fluid*
- Rarer:
  - hyperkalemia (decrease renin secretion)
  - hyponatremia (increase ADH activity)
  - nephrotic diseases

WSER research: People who had AKI on one ultramarathon were *not* more likely to get it on a subsequent ultra

- 38 runners who had undergone post-race blood analyses at multiple races among which 16 (42.1%) met the "risk" or "injury" criterion at the first race.
- 12 (75%) met the criteria at a subsequent race
- For most (56.2%) of the 16 runners meeting the criteria at the first race, the subsequent race caused less increase in serum creatinine concentration and decrement in estimated glomerular filtration rate than the first race





Horses get it too

Happy running!