Brigham and Women's Hospital
Founding Member, Mass General Brigham

Acute Kidney Injury Syndromes

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- I have no relevant financial disclosures

Objectives

- To define the common syndromes that underlie acute kidney injury (AKI) and recognize limitations of definitions

- To describe the clinical presentation and prognosis of select syndromes

AKI definition

- A group of syndromes characterized by an acute decrease in glomerular filtration.
- The degree of reduction in glomerular filtration and/or urine output provide the sole criteria for diagnosis.
- Acute Dialysis Quality Initiative (2004) and revised by the AKI network (2007) and KDIGO (2012)

KDIGO

- An increase in serum creatinine by > 0.3 mg/dL (>26.5 micromol/L) within 48 hours, or
- An increase in serum creatinine to > 1.5 times baseline, which is known or presumed to have occurred within the past 7 days, or
- Urine volume <0.5 mL/kg/hour for six hours.

- Limitations include delayed response to changes in kidney function, variability (muscle mass, age, medications, diet)

Cystatin C

- Stronger correlation with eGFR
- Smaller volume of distribution (extracellular versus TBW)
- Not influenced by muscle mass
- Faster time to doubling
- Allows earlier detection of AKI (12-24 hours compared with 12 to 72 hours for creatinine)

Epidemiology and outcomes

- High resource settings, AKI occurs in approximately 20% adult hospitalized patients
- AKI is risk factor for mortality among patients with sepsis;
- 3-5X increase in mortality at 60 days.
- Early reversal of AKI associated with I year survival is >90%
- No reversal associated with <40% survival.

Community Acquired (CA-AKI) versus Hospital-Acquired (HA-AKI)

- Different risk factors, epidemiology and outcome
- CA-AKI- present at time of admission or recognized shortly thereafter. Results from factors present in the community
- HA-AKI – Develops after 48 hours. Due to therapeutic or diagnostic intervention or a sequela of another illness
- Most studies and clinical practice guidelines pertain to HA-AKI

What are the common underlying syndromes

- Prerenal/acute tubular necrosis
- Hepatorenal
- Cardiorenal
- Rapidly progressive glomerulonephritis
- Acute interstitial nephritis
- Crystalopathies
- Obstruction

AKI-EPI Study- HA-AKI

- Prerenal/acute tubular necrosis
  - Sepsis 41%
  - Hypovolemia 34%
- Hepatorenal 3.2%
- Cardiorenal
  - Cardiogenic shock 13%
- Rapidly progressive glomerulonephritis
- Acute interstitial nephritis
  - “Drug related” – 14%
- Crystalopathies
- Obstruction (1.4%)

Hoste et al, Intensive Care Medicine 2015 41: 1411

What about CA-AKI?

- Most cases of CA-AKI are in developing countries of low- or middle income
  - Infection
  - Volume depletion from diarrhea illness
  - Poisoning, animal bites, venomous stings
  - Poor obstetrical care
  - Heat illness

ISN Oby25 Initiative

- Aims to eliminate preventable deaths from AKI by 2025
- Demonstrate the burden of AKI, particularly in low and middle income countries
- Improve diagnostic and therapeutic strategies

Mehta et al. Lancet. 2015 Vol 385 2616

Meta-analysis

- Incidence in low or middle income countries similar to high income countries.
- Increased mortality and CKD/ESKD risk
- High income – risk factors diabetes, CVD, CKD, older age
- Lower/middle income – younger age, few comorbidities

Mehta et al. Lancet. Vol 385 2016

What about CA-AKI in high income or developed countries

- Not well studied
- Outpatient population
- Incidentally detected
- Duration is not known
- Role of biopsy

Case 1

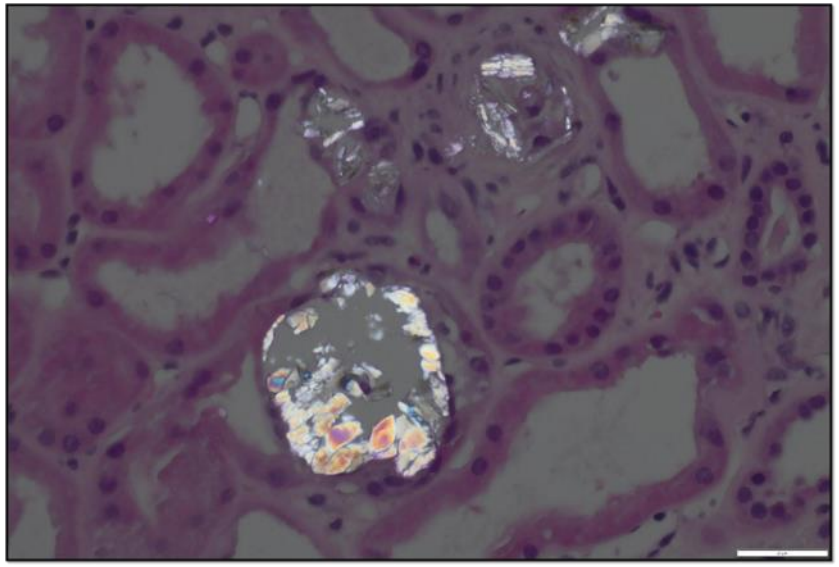
- 65-year-old man CKD eGFR 40-55 mL/min per 1.73m2 status post bilateral lung transplant and likely chronic calcineurin toxicity.
- Presented with increased creatinine that occurred over the course of 3 months. Tacrolimus level was therapeutic throughout.
- He had diarrhea attributed to small intestine bacterial overgrowth (SIBO) , with significant weight loss (30 lbs) . Treated with Augmentin.
- Ultrasound showed nonobstructing right nephrolithiasis, right renal cyst. Kidney size 12.1, 12.3 cm

Case 1

- At the time of your visit, the diarrhea has abated and he has stopped antibiotics.
- His diet is back to normal except that he is now drinking spinach smoothies and taking vitamin C gummies (1-2 daily, but occasionally takes as many as 3-4) in effort to recover his previous health status.
- He is euvolemic on exam. His creatinine remains elevated at 3.54 mg/dL.

Case 1 continued

You elect to do a kidney biopsy. Light microscopy showed widespread tubular injury with distended lumina and many intraluminal birefringent crystals under polarized light. There was interstitial fibrosis but no active cellular infiltrate. A representative micrograph is shown here.



(Micrograph and biopsy interpretation provided by Dr. Helmut R. Rennke, Renal Pathology, Brigham and Women's Hospital. Boston MA)

Case 1 continued

What is the likely cause of his persistent AKI?

A. Prolonged ischemic acute tubular injury from volume depletion

B. Drug induced acute interstitial nephritis

C. Oxalate nephropathy

D. Acute phosphate nephropathy

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Case 1 continued

A. **Prolonged ischemic acute tubular injury from volume depletion** The tubular injury observed on biopsy is commonly observed with oxalate deposition.

B. Drug induced acute interstitial nephritis Although interstitial nephritis may be observed with oxalate nephropathy, this patient did not have an active interstitial cellular infiltrate as would be expected with drug induced interstitial nephritis.

D**. Acute phosphate nephropathy** Calcium phosphate crystals are not birefringent under polarizing light, and unlike calcium oxalate, are identified with von Kossa stain. (also no risk factors in the history

Oxalate nephropathy

- Secondary hyperoxaluria results from prolonged antibiotics and excessive intake of dietary oxalate and the oxalate precursor, ascorbic acid, in the setting of volume depletion.

- Oral antibiotics alter the bowel flora with decreases in both Oxalobacter formigenes (which degrades dietary oxalate) and butyrate-forming bacteria (which maintain the intestinal mucosa and regulate intestinal oxalate transporters)

- Increased systemic oxalate absorption and hyperoxaluria cause nephrolithiasis and oxalate nephropathy . Widespread oxalate deposition strongly supports oxalate nephropathy.

Secondary Hyperoxaluria - nephrolithiasis

- Major risk factor for calcium oxalate stones
- Meta-analysis of 12 studies increased risk of stones after Roux-en-Y (RR 1.79, 95% CI, 1.54-2.10)
- Multiple studies demonstrate increased stone risk after bariatric surgery
- Multiple studies demonstrate increased stone risk with Crohn's , bowel resections, IBD, ulcerative colitis

Secondary Hyperoxaluria – nephropathy

- Less well documented – Requires biopsy. Easier to count kidney stones
- Systematic review and metanalysis (n-108)
  - 88% fat malabsorption
  - 20% dietary oxalate
  - Over half required dialysis –
  - No complete recovery
  - 42 % partial recovery
  - Excluded patients with short duration of exposure (ethylene glycol star fruit)
  - Most common presentation AKI (35%) or CKD+AKI (29%)

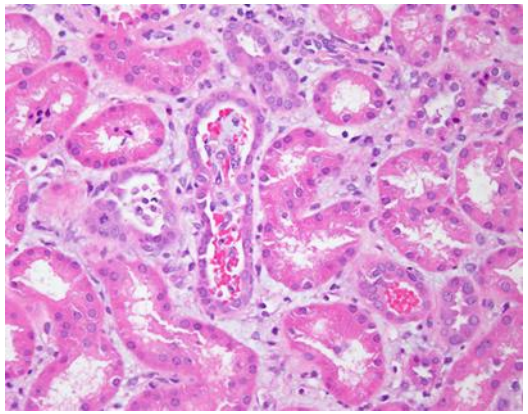
Secondary Hyperoxaluria – Treatment

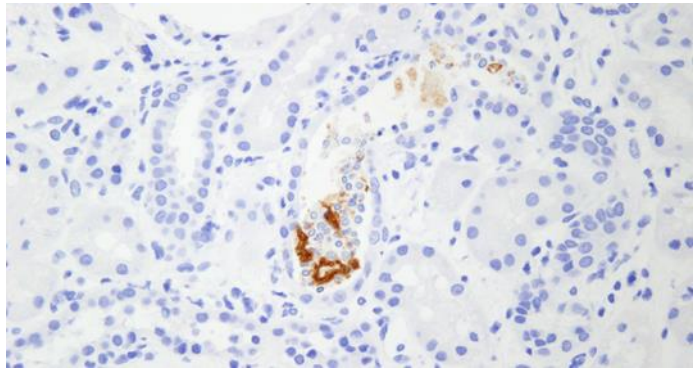
- Fluids (2.5 liters urine daily)
- Low oxalate diet
- Low fat diet
- Increased oral calcium
- Citrate

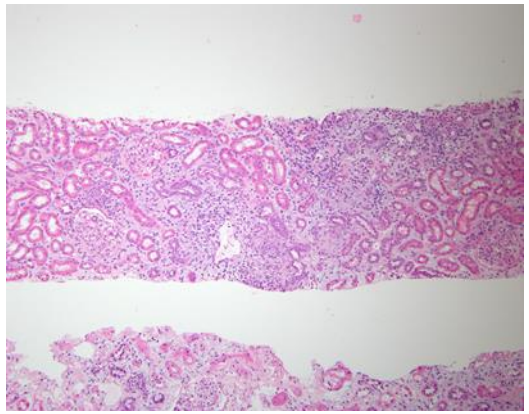
Case 2

- This patient presented to his primary care physician with nausea and vomiting and found to have creatinine of 6.1 mg/dL. Urinalysis showed 4+ heme
- Four days prior he had developed calf pain during hike). Urine turned dark after onset of pain. He took 400 mg ibuprofen during the hike
- He has had multiple episodes exactly like this (10-12 over past ten years).

Biopsy







Tubular injury with luminal dilatation, loss of brush border and flattened epithelial cells .

Tubules contained myoglobin casts.

Interstitium contained an inflammatory infiltrate of lymphocytes and plasma cells, neutrophils and eosinophils .

Case 2 continued

What was the most likely cause of his ATN ?

A. Rhabdomyolysis from vigorous exercise
B. Neuromuscular disorder
C. Hypokalemia
D. NSAIDs

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Causes of rhabdomyolysis

- Crush syndrome, limb compression
- Strenuous exercise, seizures
- Disorders of glycolysis, glycogenolysis, lipid metabolism
- Infections (Influenza A and B, COVID), coxsackie-virus, HIV, EBV, Strep, Staph,
- Heat stroke, malignant hyperthermia, malignant neuroleptic syndrome
- Hypokalemia, hypophosphatemia, hypocalcemia, DKA
- Drugs: fibrates, statins, alcohol, heroin, cocaine

Neuromuscular causes of rhabdomyolysis

- McArdle's disease
- Carnitine palmitoyle transferase deficiency
- Muscular dystrophies (Becker, limb girdle)
- Clinically evident ATN is uncommon
- Chronic tubulointerstitial nephritis has been described in patients with McArdle's , and other myopathies

Case-3

- An 81 year old woman presents with anuria, nausea and vomiting 3 days after receiving zoledronic infusion.
- Creatinine 10 mg/dL (up from 1.2 mg/dL).
- Her creatinine declines on the third day and she does not require RRT.

Case-3

- You are asked by the patient and her endocrinologist about the risks of treating osteoporosis in patients with underlying CKD. Which of the following statements are true about bisphosphonates, and zoledronic acid in particular:

Case-3

- A) The risk of AKI is high with zoledronate and palmidronate even in the absence of CKD
- B) Underlying CKD did not increase her risk of AKI
- C) AKI is an unlikely but well described side effect of zoledronic acid. While not contraindicated, it is most prudent to avoid further use in this patient.
- D) The most common histologic lesion associated with zolendronate is collapsing glomerulopathy

Case-3

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- B) Underlying CKD did not increase her risk of AKI
- C) AKI is an unlikely but well described side effect of zoledronic acid. While not contraindicated, it is most prudent to avoid further use in this patient.
- D) The most common histologic lesion associated with zolendronate is collapsing glomerulopathy

Case-3

- Pamidronate (high dose) - collapsing focal and segmental glomerulosclerosis (FSGS) in 2001 .
- Zoledronic acid (monthly infusions for myeloma or Paget's disease - AKI in 2003

- Nephrotoxicity of IV bisphosphonates is dose dependent and infusion rate dependent, and may be reduced by extending the time interval between infusions.

Case-4

- 50 year old man referred for increased creatinine (1.1□1.48 mg/dL) noted over 3 months in setting of starting ACE inhibitor.
- ACE inhibitor stopped. Repeat creatinine stable at 1.40 to 1.50 mg/dL
- PMH remarkable for new onset hypertension and osteoporosis

Case-4

- Urinalysis showed trace wbc on one occasion, sediment no casts, no crystals
- microalbumin/creatinine ratio normal
- SPEP, light chains negative, total /ionized calcium normal
- ANCA, ANA, dsDNA, anti-Ro/anti-La negative
- C3,C4 normal

Case-4

Presentation is consistent with, though not diagnostic of

A. Oxalate nephropathy

B. Acute interstitial nephritis

C. Post streptococcal glomerulonephritis

D. All of the above

E. A and B but not C

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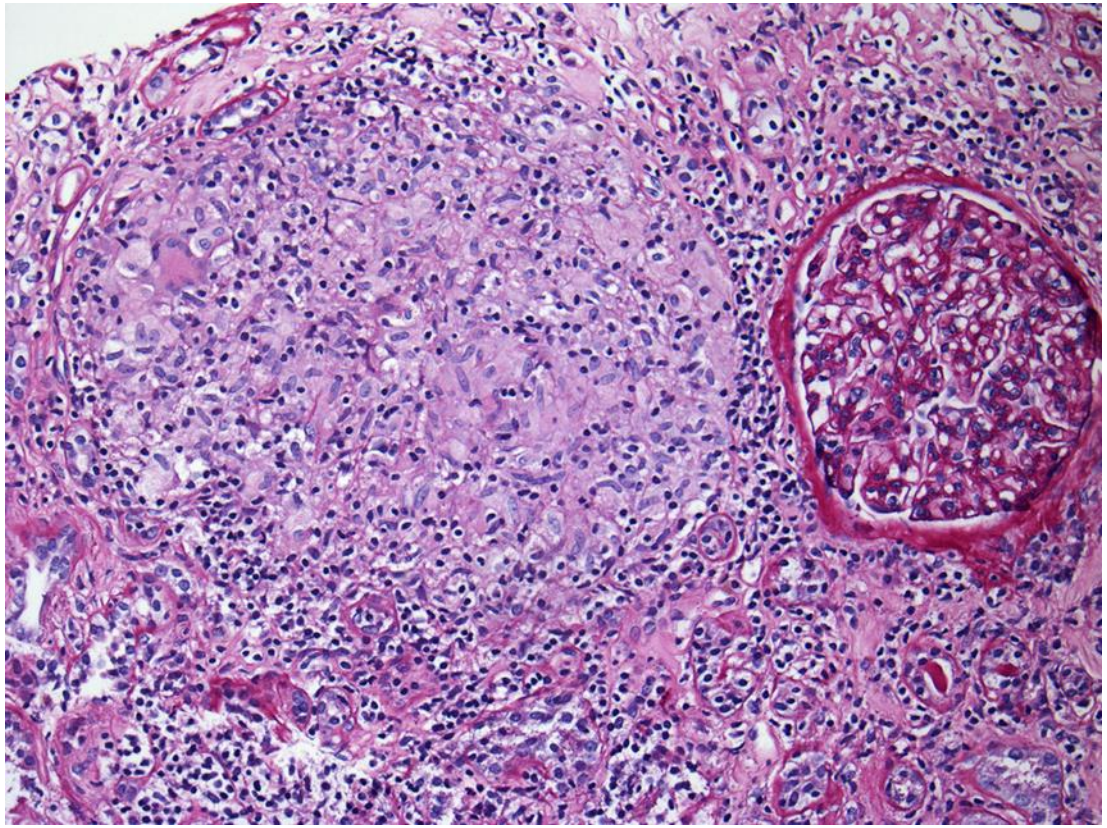
Biopsy



Chronic interstitial nephritis
A single perivascular granuloma

Acute Interstitial Nephritis

- Common cause of unexplained AKI
- Drug related in >70 %
- Infections (legionella, leptospirosis, CMV, streptococcus)
- SLE
- Sjogren's
- TINU (tubulointerstitial nephritis + uveitis) syndrome

Granulomatous Interstitial Nephritis

- Less common form of interstitial nephritis
- Drug related
- Infection - Mycobacterium, fungus (histoplasmosis, coccidiomycosis), bacteria, spirochetes, parasites.
- Tubulointerstitial nephritis and uveitis (TINU)
- Sarcoidosis
- Granulomatosis and polyangiitis (GPA)

Evaluation

- Drug review (NSAIDs, PPI, Antibiotics).
- ANCA, ACE, ANA, C3, C4, dsDNA
- Look for Infection - Mycobacterium, fungus (histoplasmosis, coccidiomycosis), bacteria, spirochetes, parasites.
- Sarcoid – Imaging (CXR, CT, bronchoscopy)
- Tubulointerstitial nephritis and uveitis (TINU)

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