Medications and Nephrotoxicity

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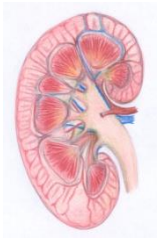

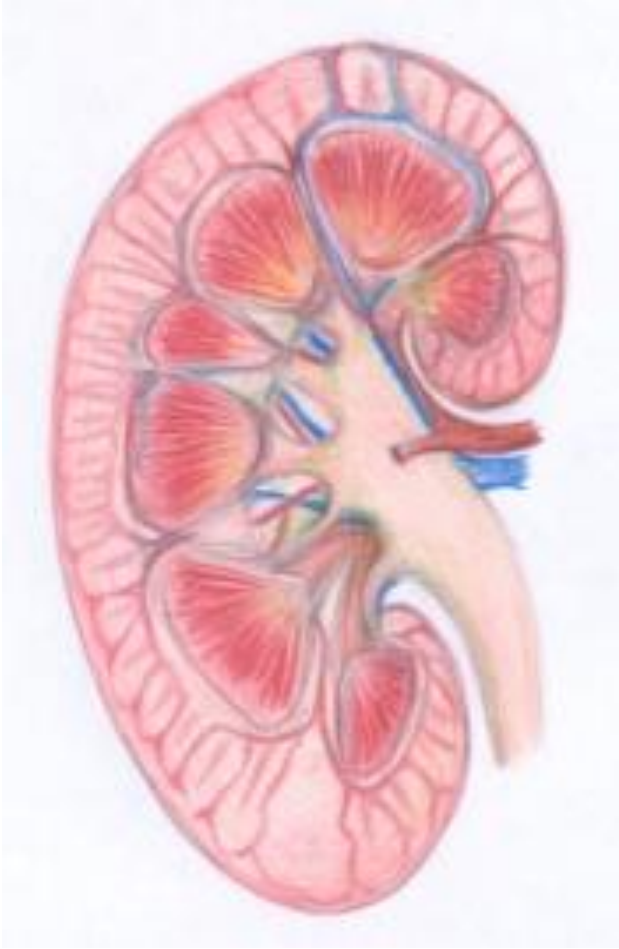

Disclosure:

I have no financial relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

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Avoid Nephrotoxins.

- every renal consult ever
- Not all nephrotoxins or nephrotoxicity is created equal
- Not all nephrotoxic agents are avoidable
- We never say “ok to resume nephrotoxins” or minimize nephrotoxins or exactly which nephrotoxins are ok

Medication Induced Nephrotoxicity

- Approximately one fifth of outpatient AKI are due to medications
  - Up to 2/3 in elderly
- With aging population and more and more medications, incidence expected to grow.
- Importance of early recognition as AKI related to medications can be predictable and or reversible

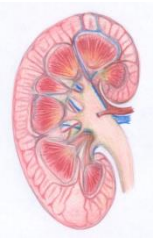
Mechanisms of Kidney Injury

- Glomerular hemodynamics
  - Examples: ACE/ARB, CNI, NSAID
- Tubular toxicity: drugs concentrated in tubules; impair mitochondrial function, tubular transport
  - Examples: amphotericin B, tenofovir, cisplatin
- Hemodynamics / ATN (diuretics, ACE, NSAID, SGLT2 inhibitors)
- Inflammation, ie AIN
  - Ex: NSAID, PPI, interferon, Au, antibiotic
- Crystal formation, tubular damage
  - Ex: trimethoprim, indinavir, acyclovir
- Electrolyte abnormalities: potassium, hyponatremia
  - Diuretics, SIADH
- Other: rhabdo (statins), thrombotic microangiopathy (clopidogrel)

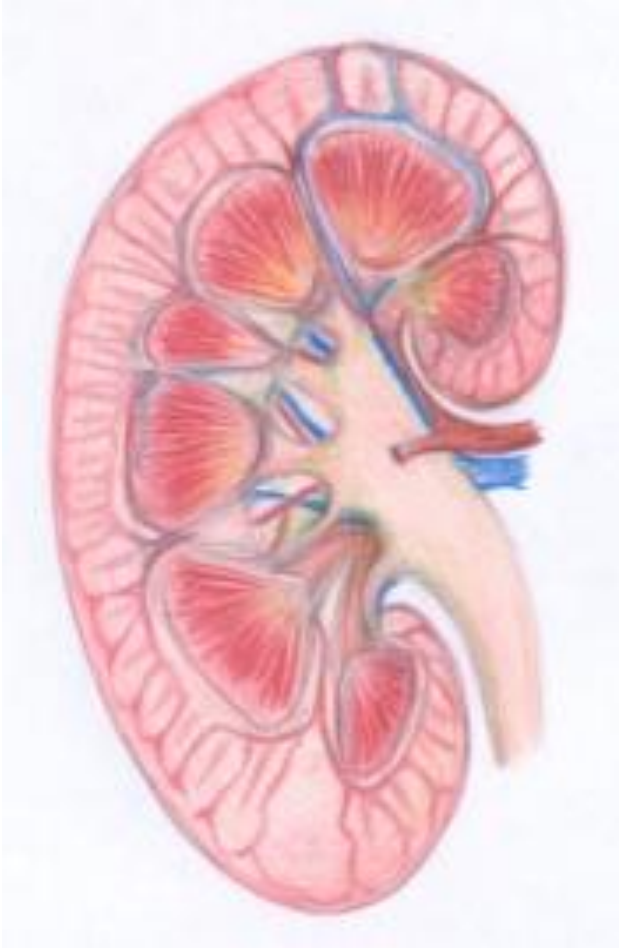
Underlying Risk Factors

- Age over 60
- Lower eGFR
- Volume depletion
- Exposure to multiple nephrotoxic agents
- Diabetes
- CHF
- Acute illness (sepsis, decompensated HF etc)

Key Points / Interim Summary



- Renal injury caused by medication can usually be reversed if detected early
- Drug-induced renal damage can be acute or chronic, prerenal, intrarenal (vascular, tubular, glomerular or interstitial) or postrenal
- There are a variety of common mechanisms for AKI (e.g. toxic, ischemic, inflammatory, or volume depletion)
- Electrolyte/acid–base abnormalities are common effects of some medications
- Medications that can cause kidney damage include diuretics, antihypertensives, immunosuppressants, antiplatelet agents, antivirals, chemotherapeutics, antibiotics and radiocontrast agents



Case #1

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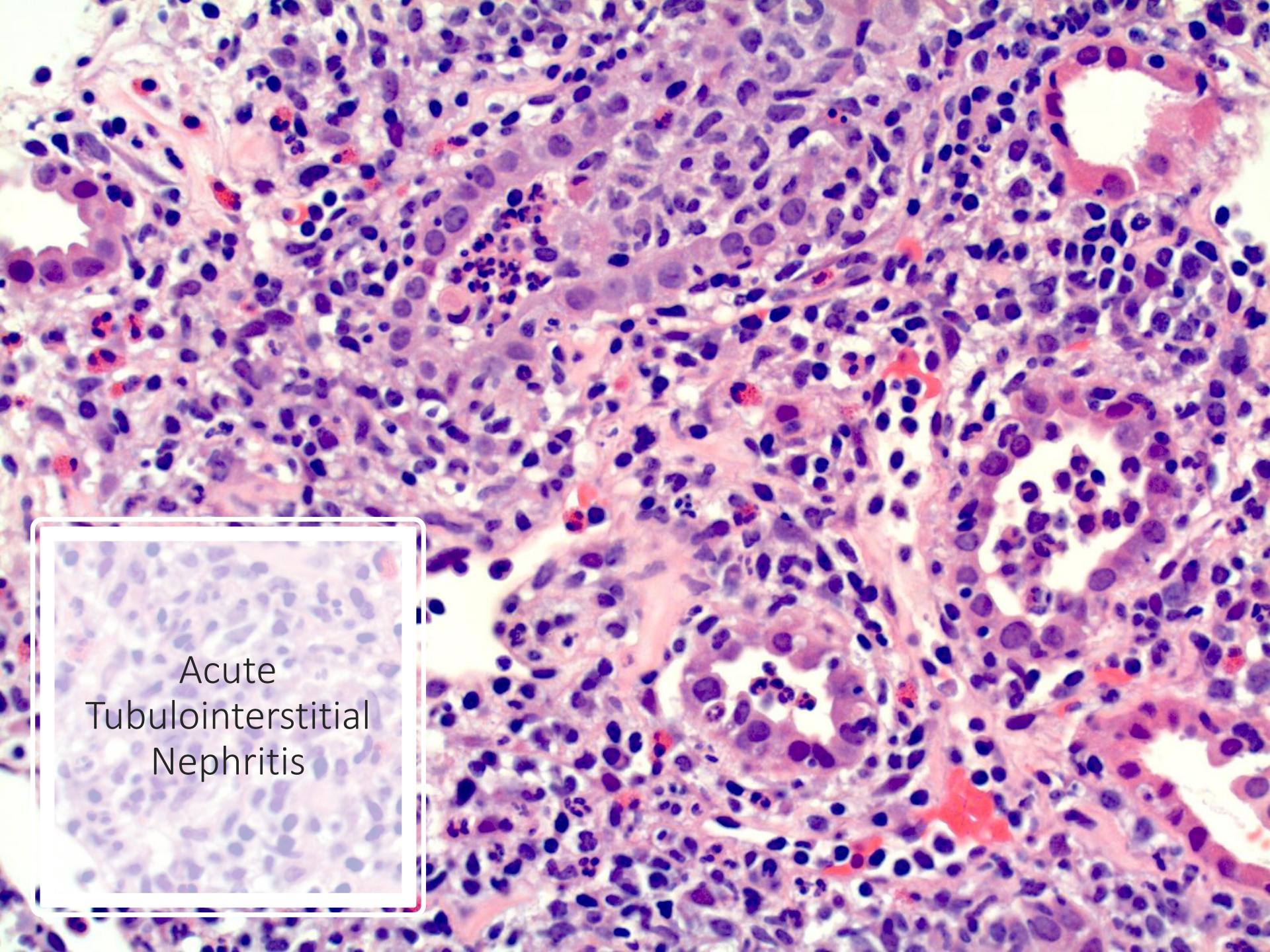
Case #1

- A 64 year old woman presents for routine, scheduled evaluation. She has a history of OA, GERD, and well-controlled HTN. Surgical history of cholecystectomy and right knee scope, both < 10 years ago.
- Meds: losartan 50 mg per day; OTC ibuprofen, 200 mg prn (usually 1-2x per week), omeprazole 20 mg daily
- Vitals WNL, exam not remarkable.
- Labs: CBC normal, Cr 1.9 (was 0.7 about 6 m ago), electrolytes normal. UA no protein, 3 wbc per hpf otherwise normal.
- Because of unexplained AKI, pt underwent kidney biopsy.


Acute
Tubulointerstitial
Nephritis

Acute Interstitial Nephritis (AIN/ATIN)

- Accounts for 20% of AKI especially of unexplained cause.
  - T cell type IV hypersensitivity
  - Less than 10% have “classic triad” (rash, fever, eosinophilia)
- Usually shows up as rising creatinine weeks or months after starting med
- Definitive diagnosis via histology on biopsy though identification of specific agent still difficult.

Interstitial Nephritis: Common Medications

- Antibiotics (penicillins/cephalosporins, quinolones, vancomycin, rifampin, sulfa)
- NSAIDs
- Proton pump inhibitors
- Immune checkpoint inhibitors
- Thiazide diuretics
- Lithium
- Anti-epileptic drugs (phenytoin, valproic acid, carbamazepine)
- Allopurinol

Epidemiology and Etiology

- Most common cause are PPIs
  - Large cohort study*: OR for PPI's for AIN of 5.16 c/w controls
  - More common in older patients, (higher PPI use with age)
  - Only a 3–5% develop AKI; common use results in a large case number
- Antibiotics (particularly β-lactams): less common than PPI but more severe
- PPIs and NSAIDs available OTC, and often used long-term / concurrently
  - NSAID cause AKI from multiple mechanisms, including AIN.
  - OTC, long term use; AIN often asymptomatic, can result in changes such as interstitial fibrosis leading to CKD.

**Kidney Int. 2014:86*

AIN Diagnosis: A catch-22

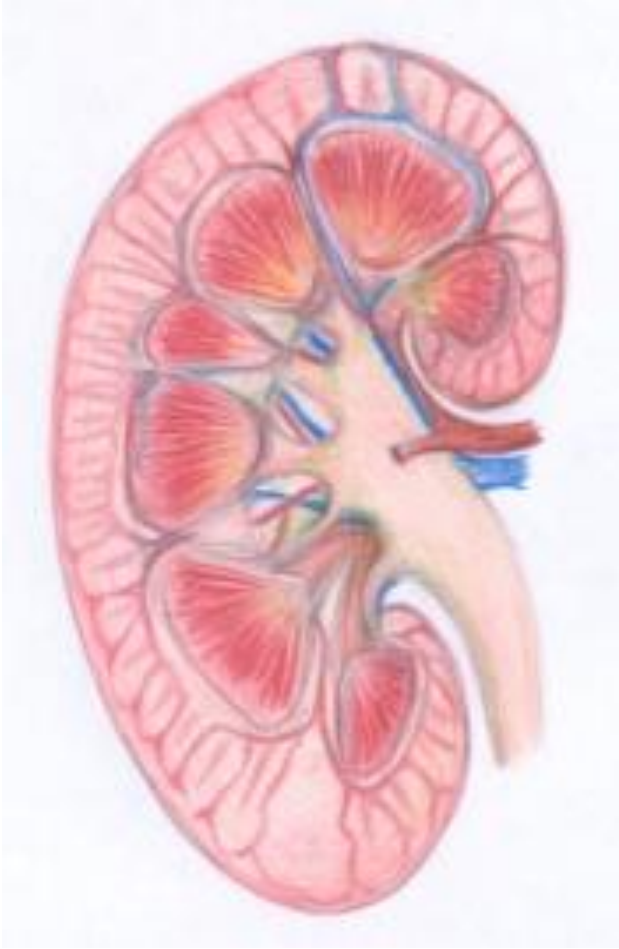
- Difficult clinical diagnosis, often delayed.
- Most patients have nonspecific or even no symptoms, rare to have “classic symptoms” of rash, fever, flank pain
- Serum, urine eos, urine microscopy all have poor sensitivity and specificity
- Traditional imaging (US, CT) not useful.
- Gallium-67 scan:
  - Retrospective analysis (n=76; 23 with AIN), renal ^{67}Ga uptake showed an AUC of 0.75.
  - Only 20 of 76 patients had gold standard (biopsy) to rule in or out AIN
  - Investigators not blinded to ^{67}Ga results
- Improves with discontinuation of agent; depends on high index of suspicion
- Lack of biomarker and diagnostic challenges, need for biopsy delays diagnosis, which is associated with poorer outcome.
- Diagnosis (biopsy) often delayed; delay can result in permanent damage

Krishnan N, Perazella M.
Iranian J Kidney Dis 2015

Drug-induced AIN treatment

- Stop culprit drug: sometimes not that easy to determine.
- Retrospective evidence suggests steroids beneficial[1]
  - Retrospective; confounded
  - Standard of care even as analyses done (impossible to conduct RCT)
- Two retrospective studies showed no benefit though steroid group had worse kidney function[2] or treatment initiated late[3]
- Larger, more standardized (with respect to histology and creatinine) studies with steroids initiated quickly after diagnosis showed better outcomes with steroids[4-6]
- Biopsy useful: more fibrosis suggests poor response to steroids

[1] Moledina/Perazella CJASN 2017 [2] Valluri QJM 2015 [3] Clarkson NDT 2004
[4] Prendecki Clin Kidney J 2017 [5] Raza Nephrology 2012 [6] González KI 2008



Case #2

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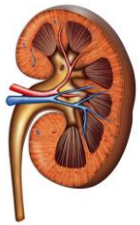
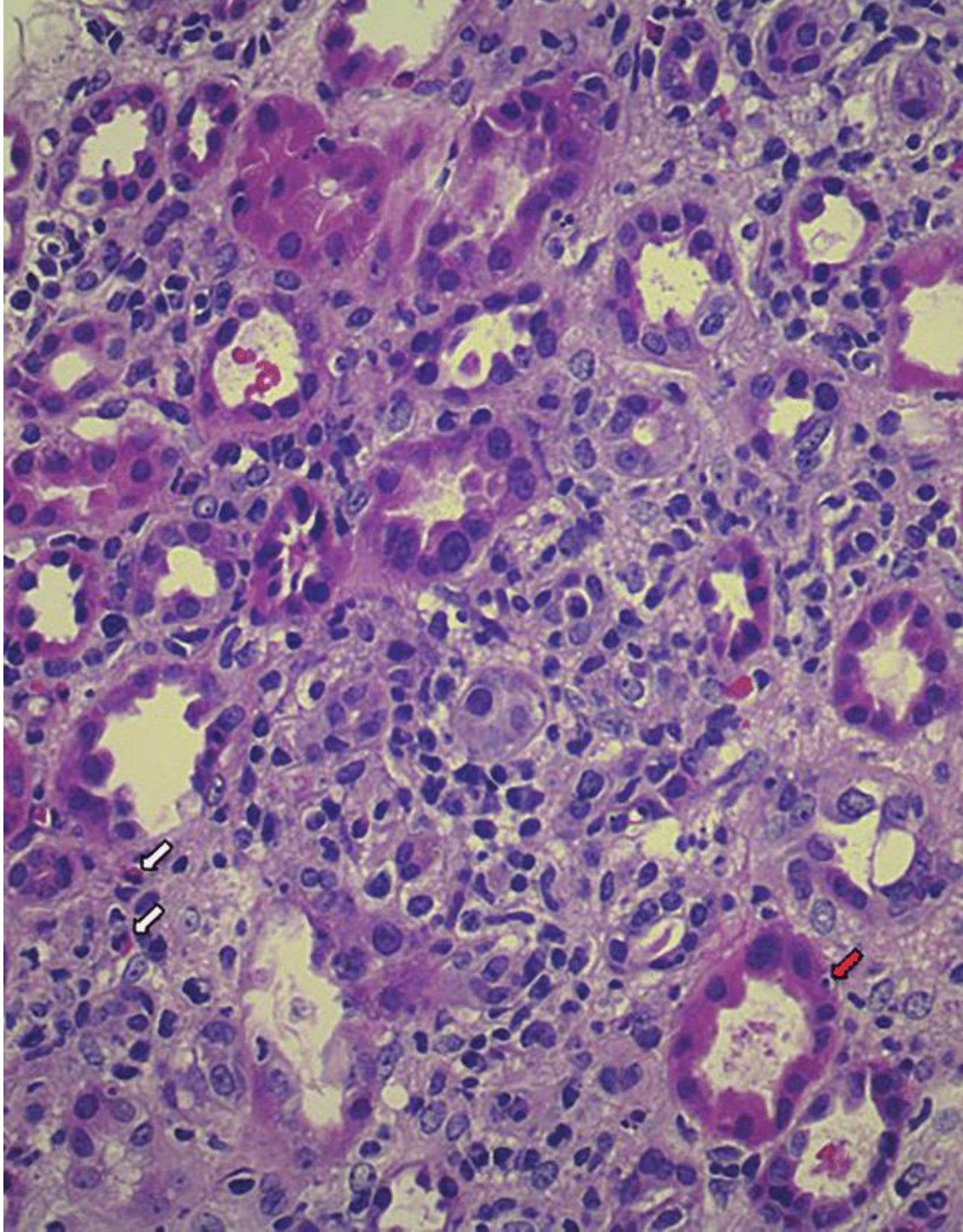
Case 2

- 60 year old female with depression, surgical hypoparathyrodism, vitamin B12 deficiency, metastatic melanoma, presents for evaluation of elevated creatinine. The creatinine began to rise after the initiation of nivolumab.
- Meds include B12, calcitriol, citalopram, CaCo3, nivolumab.
- Labs show cr 2.2 (baseline 0.9). UA 1+ wbc, 0 RBC and 1+ protein; no casts seen on urine microscopy. CBC wnl. Renal US wnl. Urine culture negative.
- A biopsy was done to evaluate cause of elevated creatinine.



Biopsy

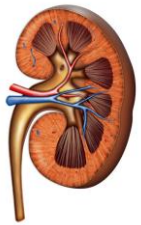
- Light microscopy (right): patchy interstitial inflammatory infiltrate, mostly mononuclear cells with some eosinophils
- There was associated acute tubular damage
- Glomeruli essentially normal; some tubules with protein
- Minimal tubular interstitial fibrosis and tubular atrophy
- Mild arteriolosclerosis



Checkpoint Inhibitors

- Checkpoint inhibitors such as nivolumab inhibit ligands which cancer cells express to suppress T cell activation
- Allows host immune system to avoid cancer cells' ability to suppress T cell activation (tumor infiltrating lymphocytes)
- Host immune cells can then identify and eliminate cancer cells
- Two categories: ipilimumab/tremelimumab (CTLA-4–blocking Ab) and nivolumab/pembrolizumab (PD-1–blocking Ab)
- These drugs have proven effective in a variety of cancers
  - Associated with a immune related side effects including in the kidney

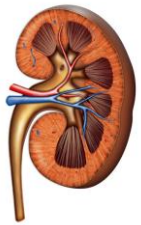
Perazella, CJASN 14: 1077–1079, 2019



Checkpoint Inhibitor and AKI

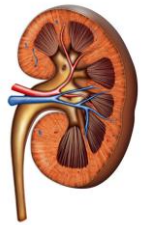
- Several case series of AKI with checkpoint inhibitors
- AKI occurred 1- 16 months after initiation (median 14 weeks)
- Biopsy most often shows AIN; also TMA, GN, minimal change
- Most have good outcomes with discontinuation; some required steroids
- Importance of biopsy in these cases, as DI-AIN is only one possible cause
- Accurate diagnosis so that effective drug is not discontinued
  - AKI can occur from a variety of causes in cancer patients (nephrotoxic or other ATN, drug-induced AIN, GN, crystal nephropathy, obstruction, etc

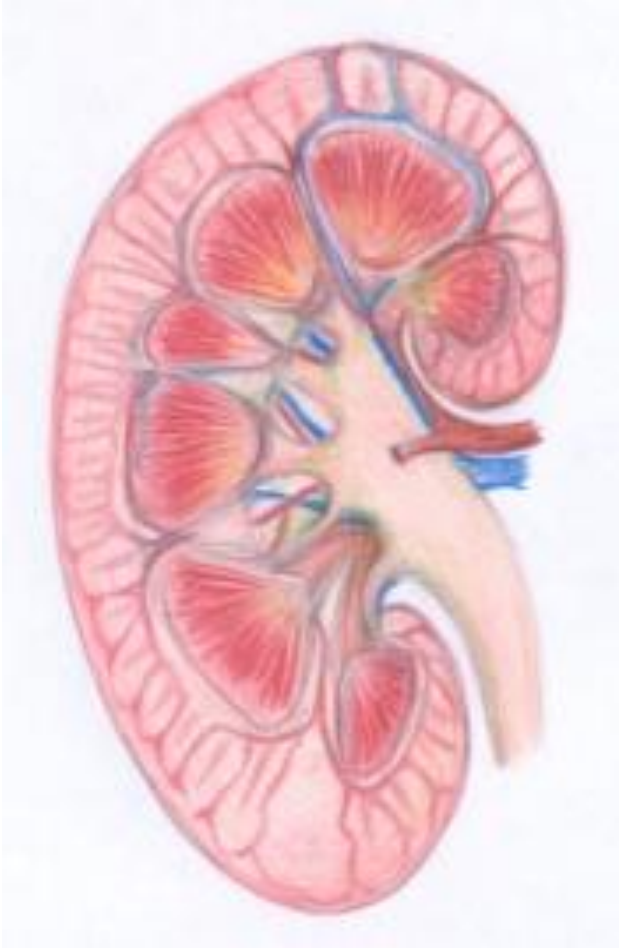
Perazella, CJASN 14: 1077–1079, 2019



Management

- Mild AKI: monitor
- Moderate/Severe: Steroids
- Restarting checkpoint inhibitor possible; some initiate with low dose steroids but no good data in this area.
- Our patient had AIN, with minimal fibrosis / chronic changes
- After discussion with oncology, we stopped the nivolumab as disease was quiescent
- Cr quickly improved to ~ 1.2; steroids were considered but not initiated





Case #3

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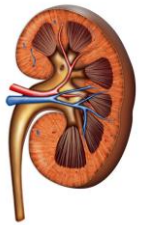
Case #3

- 67 year old female with type 2 diabetes, complicated by nephropathy, retinopathy and peripheral vascular disease comes back for followup to wound clinic, where she had been initially evaluated last week with a severe, deep soft tissue infection on the sole of the right foot.
- Medications: empagliflozin, insulin, metformin, lisinopril, gabapentin, trimethoprim-sulfa (started last week).
- UA shows 2+ protein, otherwise negative. Serum creatinine is 6 (baseline 1.7), serum potassium is 6.1; rest of chemistries and CBC are normal.

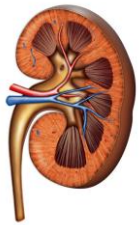


Trimethoprim-Sulfamethoxazole AKI

- VA study showed 11.2% of over 500 veterans treated with TMP-SMX had AKI (J Antimicrob Chemother. 2012)
  - AKI resolved after discontinuation; one patient required HD.
  - Pyuria uncommon and no patient had eosinophiluria
  - Risk factors identified included HTN, CKD and DM2

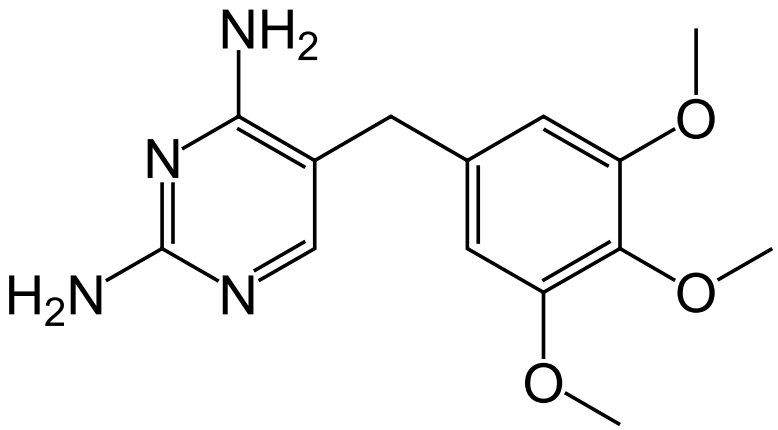
- Trimethoprim also causes hyperkalemia, similar to other K-sparing diuretics

- Concurrent use of ACE/ARB nearly quadruples risk of hyperkalemia, even with low-dose, prophylaxis dose (Intern Med. 2016)

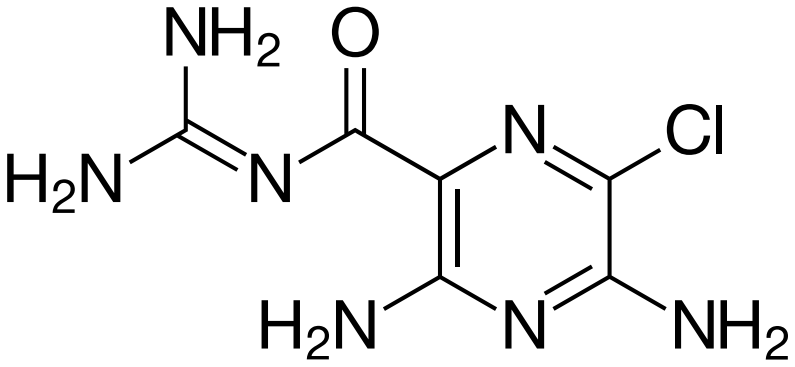


Trimethoprim-Sulfamethoxazole: Hyperkalemia

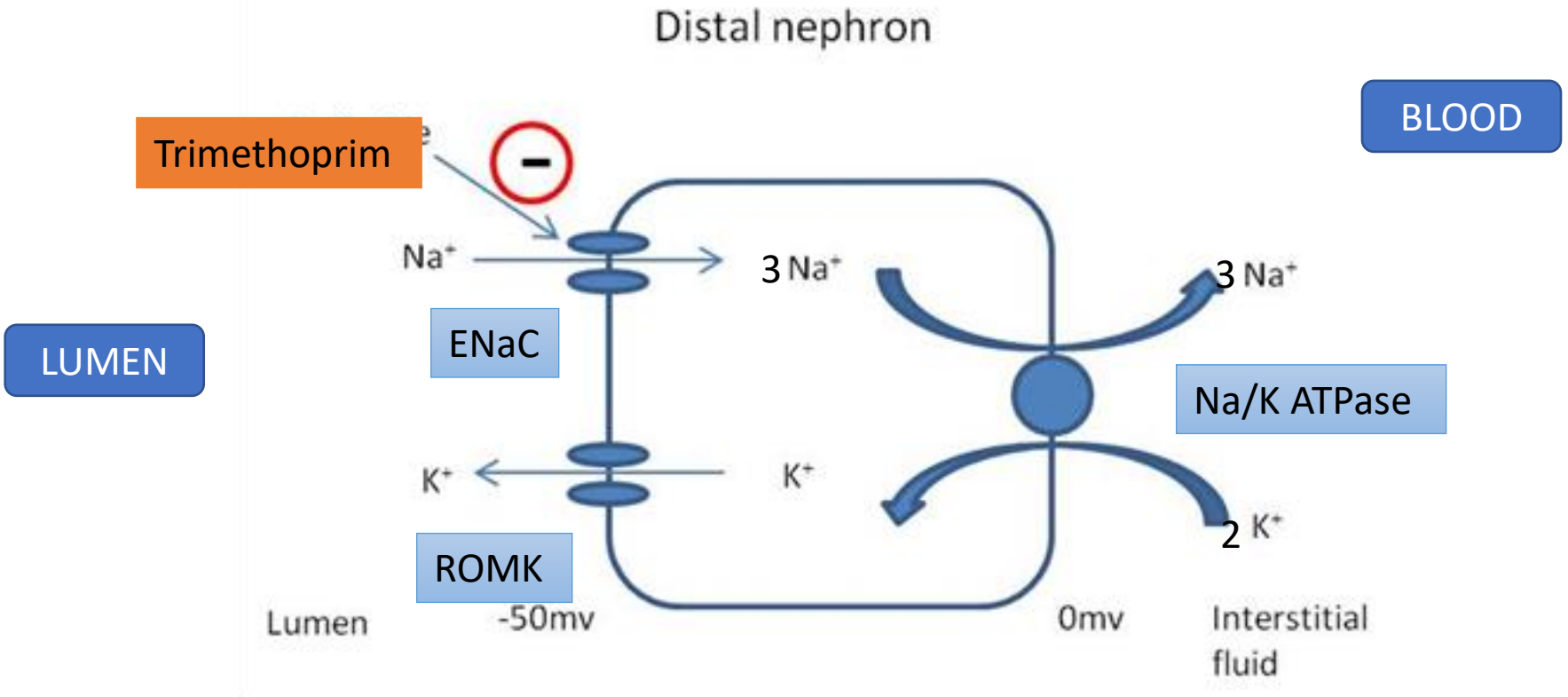
TRIMETHOPRIM



AMILORIDE

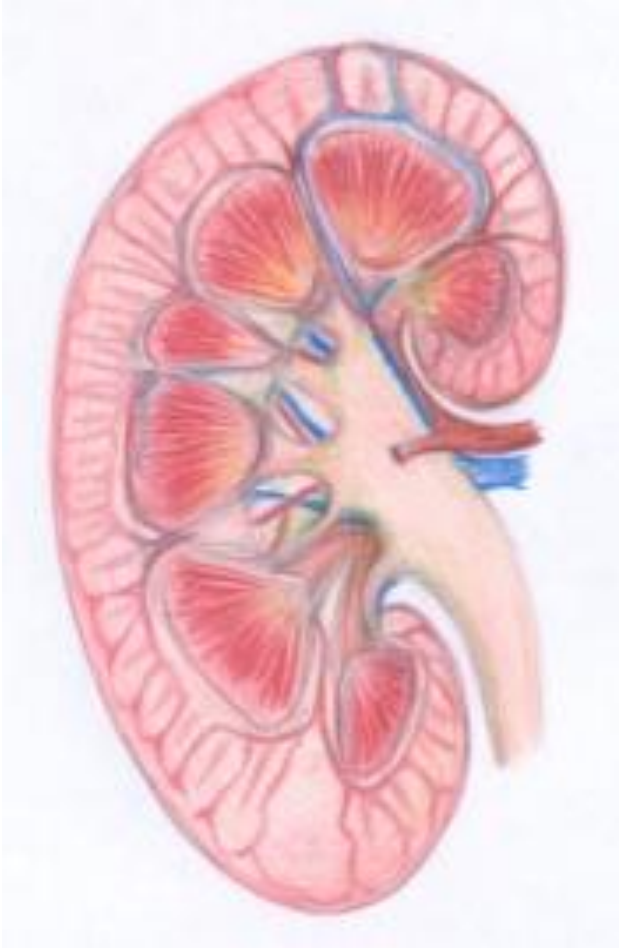


Trimethoprim and Hyperkalemia



Trimethoprim, amiloride, and triamterene all block sodium channels in distal nephron*

*N Engl J Med 1993; 328:



Case #4

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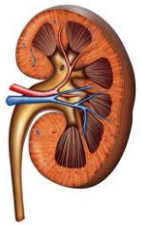
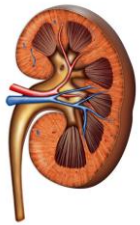
Case # 4

- 73 year old female with type 2 diabetes, HTN, depression presents to her primary care physician for mild confusion noted by family. Family states she ‘just doesn’t seem herself’ and is maybe a little unsteady on her feet. This began about 2 weeks ago.
- Medications: empagliflozin, metformin, lisinopril, chlorthalidone, sertraline



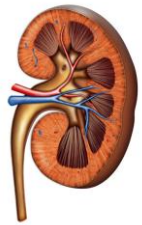
Case # 4 continued.

- Exam unremarkable although she does seem a little confused.
- Routine labs show serum Na 122, K 3.4, Cl 70, BUN 12, Cr 0.7, bicarb 25, glucose 158. TSH wnl, Six weeks ago the sodium was 131
- On further questioning, it appears the sertraline was added about 2 months ago.



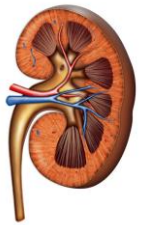
Hyponatremia

- Defined as serum sodium less than 130 mEq/L
- One of the more common electrolyte imbalances, and probably the scariest especially to non-nephrologists
- Important to rule out common causes (hypovolemia, pseudohyponatremia from hyperglycemia, lipids, hypothyroidism)
- Symptoms are generally nonspecific
  - Nausea, malaise, HA, confusion
  - Severe ([Na+] > 120) is life-threatening from CNS effects: seizures, herniation
  - More mild hyponatremia can cause cognitive issues, balance, higher incidence of falls, fracture etc.



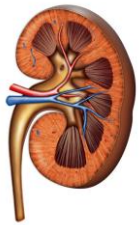
Hyponatremia from medications

- Commonly associated medications include thiazide diuretics, SSRI, PPI, antiepileptics, antipsychotics
- Many of these agents stimulate or potentiate effects of ADH
- Thiazides predispose to volume depletion (ADH) as well as inhibit ability to excrete free water
- Often multifactorial, including polypharmacy, clinical conditions (volume depletion, heart failure, cirrhosis, malnutrition)
  - "Tea and toast": Poor po intake reduces ability to excrete free water



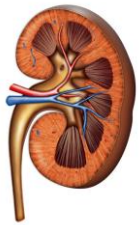
Hyponatremia from SSRI

- Well documented in reports (case series, manufacturer reports)
- All SSRI associated with increased risk of hyponatremia
  - Median time to developing hyponatremia 9-13 days, range up to 120 days
- Incidence varies by study, ranges from 1% to nearly one third; probably around 15%
  - Higher risk in elderly, female patients, lower baseline [Na^+]
  - Concurrent treatment with other meds or comorbid conditions that cause hyponatremia
- Generally resolves in 2 weeks on discontinuation of drug



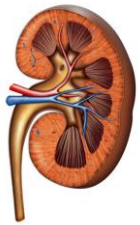
ADH and hyponatremia with SSRI

- The mechanism is not 100% clear
- Pattern of hyponatremia with high U Osm & Na suggests ADH effect (SIADH)
- Serotonin can cause increased ADH release through 5-HT2 and 5-HT1c receptors
- SSRI may also increase renal ADH responsiveness
- SSRIs also inhibit norepinephrine reuptake which stimulates ADH release by α1-adrenergic receptors
  - SNRI's also associated with hyponatremia & SIADH like syndrome



Thiazides and Hyponatremia

- Very common cause of hyponatremia
- Risk factors include low muscle mass, low protein intake, meds that cause hyponatremia (ie SSRI/SNRI, NSAID), elderly, female, comorbid conditions that predisponse to hyponatremia (DM2, cirrhosis, CHF)
- Cause volume depletion and increase effect of ADH
  - Volume depletion increases ADH
- Combination of decreased ability to excrete free water (dilute urine) due to inhibiting distal sodium NaCl reabsorption.
  - Contrast with loops, that have their effect more proximally in nephron, and don't cause hyponatremia
- Decreased prostaglandins (either with age or NSAID) can inhibit urinary free water excretion



Conclusions

- Drugs can induce nephrotoxicity by a variety of mechanisms
- Nephrotoxicity can be reversible in many cases if picked up early
- Nephrotoxicity increasing with aging population, increased comorbidities and a variety of new agents
- A high index of suspicion and knowledge of pharmacologic mechanisms is key to early identification and intervention in medication related kidney toxicity.