Drug-Induced Acute Kidney Injury

Keith Miller BEng, BScPharm, Pharm D, ACPR, CDE

Clinical Pharmacist Nephrology- GRH

Disclosures

- Advisory Board Member: Otsuka

Commercial Support Disclosure

- This presentation has received no financial or in-kind support from any commercial or other organization

Learning Objectives

By the end of this presentation participants should be able to:

- Define Acute Kidney Injury
- Understand the pathogenesis and clinical pathologic manifestation of drug induced kidney injury
- Identify three types of tubulointerstitial injury and understand their mechanisms of nephrotoxicity
- Highlight common medication culprits for acute kidney injury
- Understand and recommend preventative and treatment strategies to manage drug induced AKI

Acute Kidney Injury Definition

- An abrupt decrease in kidney function (with or without other acute or chronic kidney disease/disorders)

- Broad clinical syndrome encompassing various etiologies
  - Includes both kidney-specific disease (i.e. acute interstitial nephritis) or extra-renal pathology (i.e. sepsis)

- Standard criteria have been established (KDIGO guidelines):
  - Increase in serum creatinine (SCr) by 1.5 times baseline within 7 days OR
  - Increase in SCr by 26.5 µmol/L within 48 hours OR
  - Oliguria (urine volume <0.5 mL/kg/hr for at least 6 hours)

KDIGO Clinical Practice Guideline for AKI 2012

Why we should be aware of AKI

- Epidemiology
  - Accounts for 19-27% of all hospitalized cases
  - 20-60% of critically ill patients experience AKI
    - ¼ cases associated with nephrotoxic medication exposure
- Risks

Table 6 | Causes of AKI: exposures and susceptibilities for non-specific AKI

Exposures	Susceptibilities
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	CKD
Cardiac surgery (especially with CPB)	Chronic diseases (heart, lung, liver)
Major noncardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

CKD, chronic kidney disease; CPB, cardiopulmonary bypass.

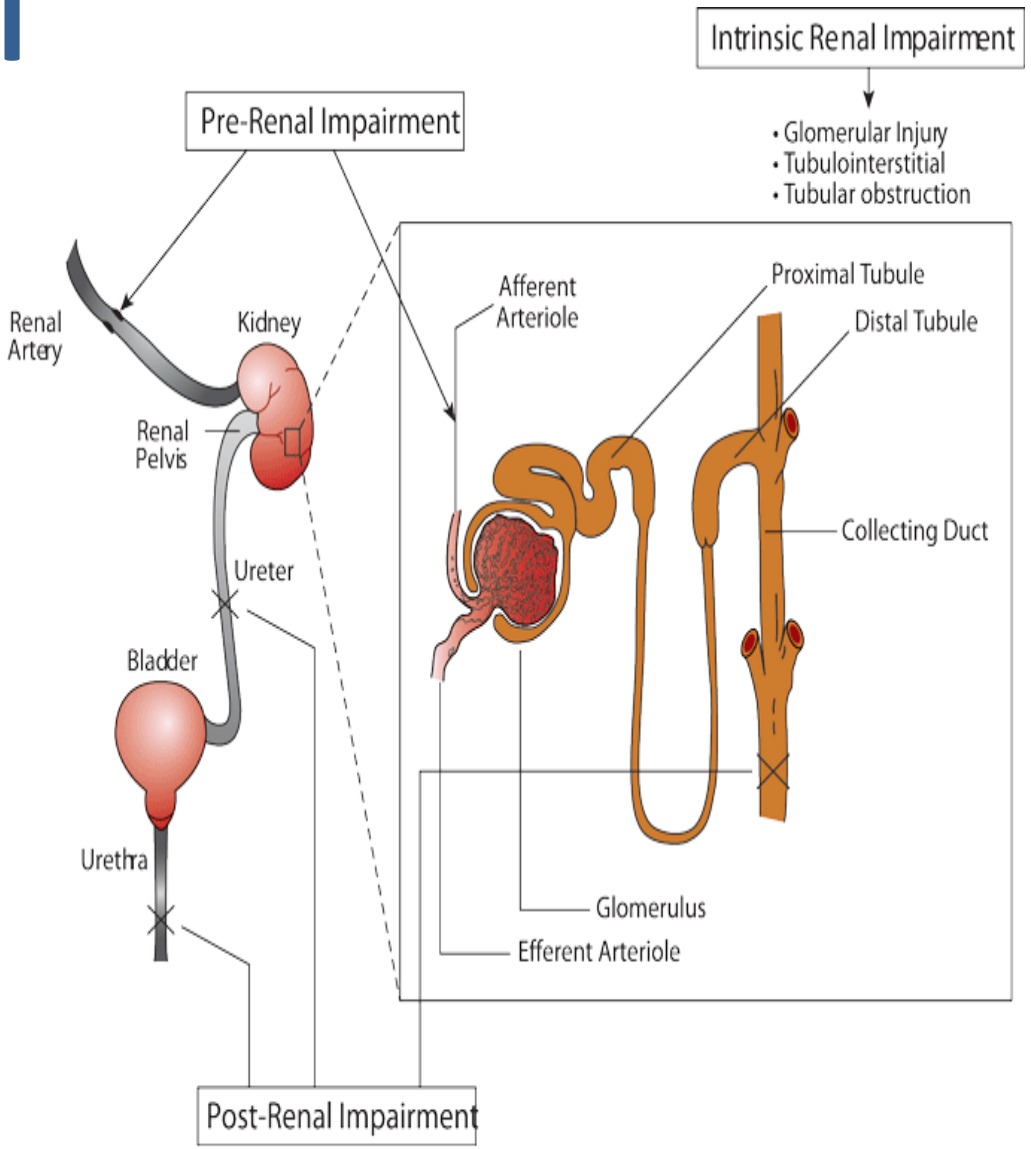
Int. J. Mol. Sci. **2021;** *22:* 6109.
Crit Care Med. 2010; 38: S169-S174
KDIGO 2012 AKI Guidelines

Buckets of AKI

Pre-Renal
Inadequate renal perfusion due to volume deficiency, Hemodynamically Mediated

Intra-Renal
Structural Damage within the kidney, Acute-Tubular Necrosis, Acute Interstitial nephritis

Post-Renal
Crystal nephropathy, Ureteral obstruction, BPH, kidney stone in solitary kidney, drug related urinary retention



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

Question

Non-steroidal anti-inflammatory drugs can cause acute kidney injury by:

A) Hemodynamically mediated AKI (pre-renal)

B) Acute tubular injury (intra-renal)

C) Acute interstitial nephritis (intra-renal)

D) All of the above

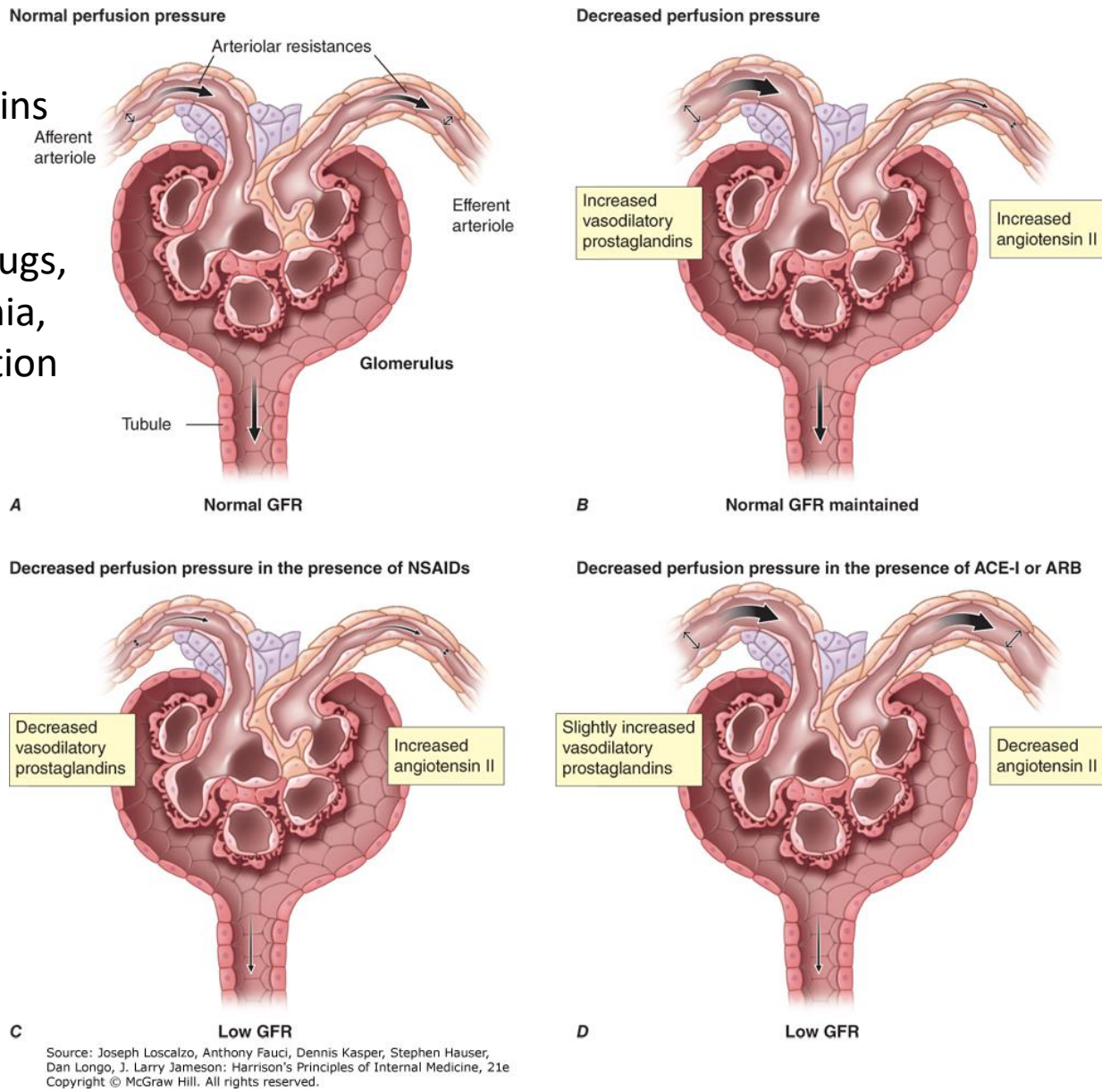
Pre-Renal AKI – Hemodynamically mediated

NSAIDs

- Inhibit synthesis of prostaglandins preventing afferent arteriole vasodilation
- Risks: Age, CKD, nephrotoxic drugs, volume depletion, hypercalcemia, effective arterial volume depletion (HF, cirrhosis)

RAAS Blockade (ACE-I/ARB)

- Reduce angiotensin-II causes dilation of efferent arteriole
- Risks: Renal artery stenosis, volume depletion, HF, CKD, nephrotoxic drugs
- Moderate rise in SCr < 30% tolerated
- Start low, titrate slow



Question

76 year old male with eGFR 35 (Stage 3b) CKD, HTN, GERD taking perindopril, pantoprazole and tamsulosin, continues to experience pain despite taking acetaminophen 500 mg BID and requires further pain control.

A NSAID can safely be used in this patient

A) True

B) False

*Nephrotoxicity**	Stage 1-2 CKD	Stage 3 CKD	Stage 4 CKD	Stage 5 CKD, No KRT
AKI	Low risk, similar to	Low risk, similar to non-elderly general	At least moderately increased risk	High risk compared with general
Data S				
Recommen-dations	Short-term use for ≤5 days acceptable**. Long-term use also acceptable on case-by-case basis**, with close monitoring for nephrotoxicity and for development of risk factors for nephrotoxicity as in Table 3.	on a case-by-case basis with close monitoring**. In patients with underlying hyperkalemia, should consider NSAIDs contraindicated.	Would consider NSAIDs as absolutely contraindicated except under circumstances of palliative care.	

2 **Don't prescribe nonsteroidal anti-inflammatory drugs (NSAIDS) in individuals with hypertension or heart failure or CKD of all causes, including diabetes.**

https://choosingwiselycanada.org/recommendation/nephrology/

Am J Kidney Dis. 76(4):546-557.

Pre-Renal AKI – Hemodynamically mediated

Management NSAID induced AKI

- Discontinue therapy
- Avoid other nephrotoxic drugs
- Kidney function generally recovers in 3 – 5 days
- Severe cases of NSAID nephrotoxicity can cause acute tubular necrosis
- Avoid dehydration

Case

You provide discharge counselling to a patient following her admission for acute kidney injury and you inform her that her ARB was stopped and that it needs to be reassessed by her GP. When can the ARB be safely resumed?

Pre-Renal AKI – Hemodynamically Mediated

When to resume ACEi/ARB

- Reassess indication for the drug
- Discontinue if contraindicated (severe bilateral renal artery stenosis)
- Use alternative antihypertensive if ACEi/ARB was prescribed for essential hypertension as risks likely outweigh benefit
- Resume in cases with proven benefit (HFrEF, ACS, CKD)
- Wait for SCr to stabilize (3 - 6 weeks)
- Resume at low dose and titrate slowly checking SCr and K regularly
- Consider decrease in dose with significant increase in SCr (greater than 30%) or stop if K elevated (greater than 5.5 mmol/L)
- Routinely check labs once stabilized on target or maximally tolerated dose

https://www.thinkkidneys.nhs.uk/aki/resources/primary-care

Clinical Resource, *Using and ACEI or ARB After Acute Kidney Injury. Pharmacist's Letter/Prescriber's Letter.* February 2019.

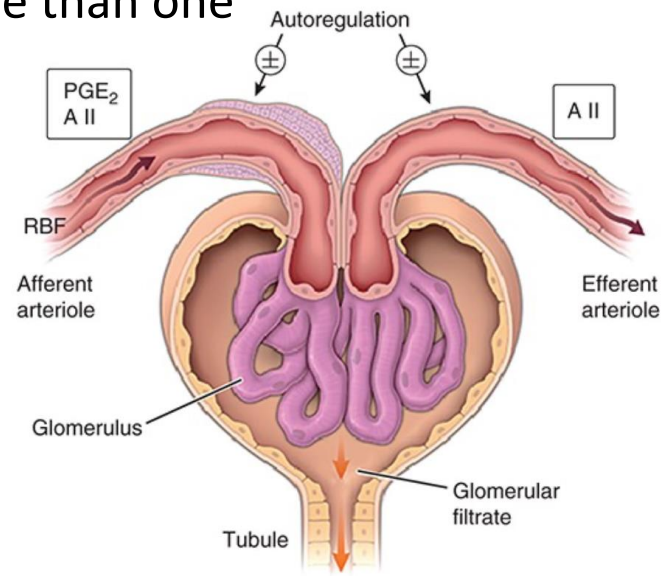
Pre-Renal AKI – Hemodynamically mediated

Diuretics

- Combined with significant volume depletion (diarrhea, sweating, bleeding) or compromised cardiac output, cirrhosis or nephrosis
- Concomitant use of more than one diuretic class

Vasodilators

- Rapid decrease in blood pressure impairs mechanism to maintain renal filtration



Calcineurin Inhibitors

- Vasoconstriction of afferent and efferent arterioles (increase endothelin and thromboxane A2 and decrease prostaglandin)
- Effect is dose related, monitor drug levels

Intra-Renal AKI

Direct damage to renal tubules, glomerulus, vascular structures or interstitium

- Drug induced direct acute tubular injury (Acute Tubular Necrosis)
- Inflammation of the tubulointerstitium (Acute interstitial nephritis)

Recovery time is weeks to months; may require temporary renal replacement therapy (RRT)

Intra-Renal AKI – Acute Tubular Necrosis (ATN)

- Direct tubular injury or ischemia by apical contact with drugs or uptake of drugs leading to the shedding of the proximal or distal tubule lumen causing tubular obstruction or inability to reabsorb electrolytes

- Risk Factors: Advanced age, preexisting kidney disease, intravascular volume depletion, diabetes, concomitant nephrotoxic drugs, prolonged use, excessive blood levels.

- Most common type of drug induced kidney injury

- Common drug culprits
  - Antibiotics
  - Antifungals
  - Radiocontrast agents
  - Bisphosphonates

Intra-Renal AKI – ATN

Medication Class	Specific Medication	Preventative Strategies	Adjust dose for underlying eGFR
Antibiotics	Aminoglycosides (gentamicin, neomycin, amikacin)	Once daily dosing Use tobramycin over gentamicin	
	Vancomycin (+/- piperacillin-tazobactam)	Therapeutic drug monitoring Avoid combination with pip-tazo Use alternative agents	
	Colistin/polymyxins	Avoid prolonged use	
Antifungals	Amphotericin B	Use lipid or liposomal forms IV isotonic crystalloid hydration	
Antiviral Agents	Cidofovir, tenofovir, adefovir, foscarnet	Screen for tubular toxicity to identify early injury Use alternative agents	

CJASN 17: 1220-1233, 2022

Intra-Renal - ATN - Antibiotics

Pathogenesis

- Induces reactive oxygen species → affect cell metabolism
- Increase mitochondrial stress → release cytochrome-c → cellular stress and apoptosis

Vancomycin

- Rate of AKI 0 % (no concomitant nephrotoxins) to 20% (with tazocin)
- AKI occurs within 4-8 days of therapy
- Improves with drug withdrawal
- Formation of Vancomycin casts (uromodulin + vancomycin → non-crystalline vancomycin aggregates) → obstruct tubular lumens → tubular necrosis and inflammation
- Cast formation promoted by high urine level of drug and low PH

Question

Vancomycin induced nephrotoxicity is caused only by supratherapeutic levels?

A) True
B) False

Intra-Renal-ATN-Antibiotics

Monitoring is the key to prevention

- Target vancomycin trough less than 20 mg/L
- Target Vancomycin AUC less than 600 mg*h/L

AUC monitoring associated with lower incidences of kidney injury. (longer intervals and lower doses)

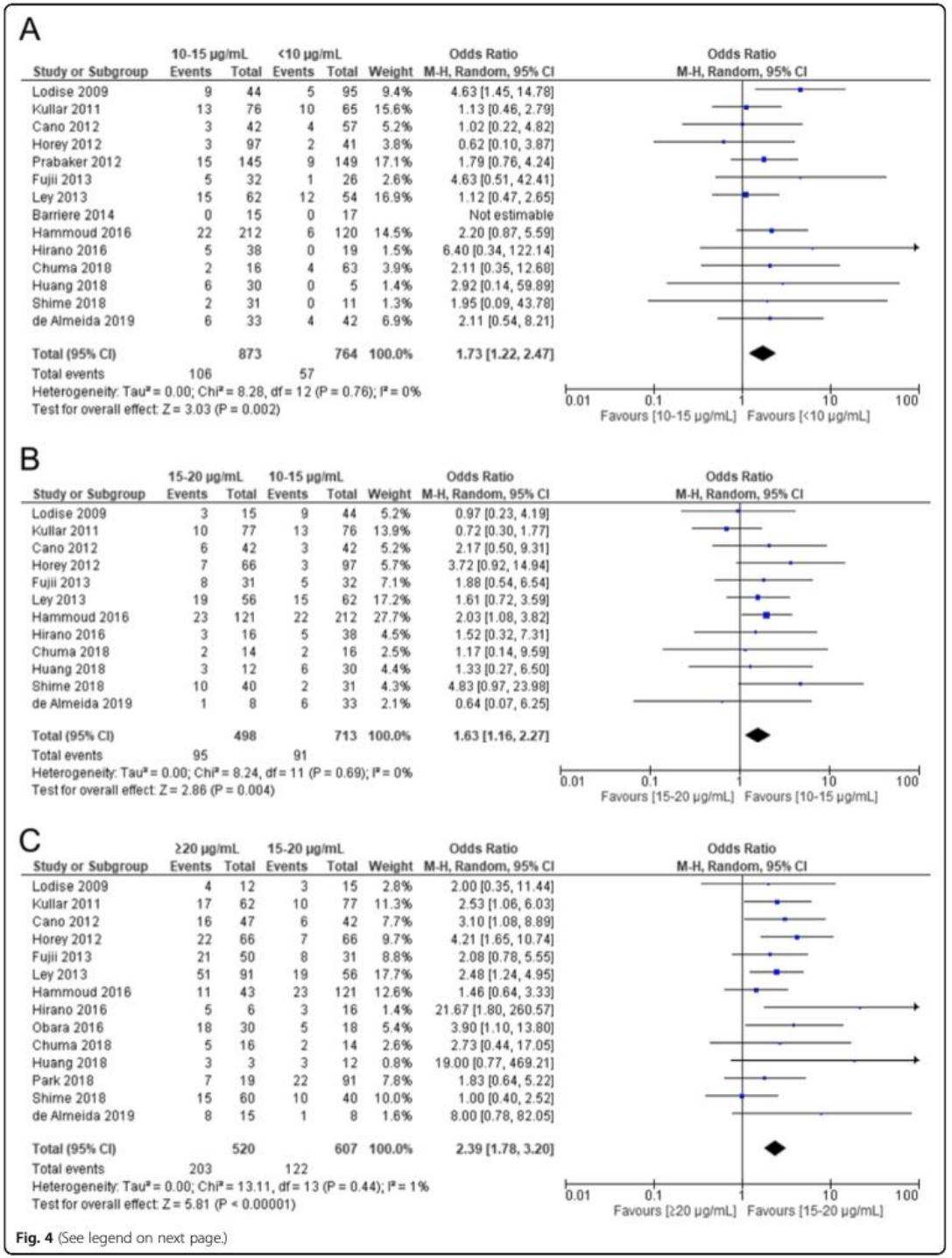


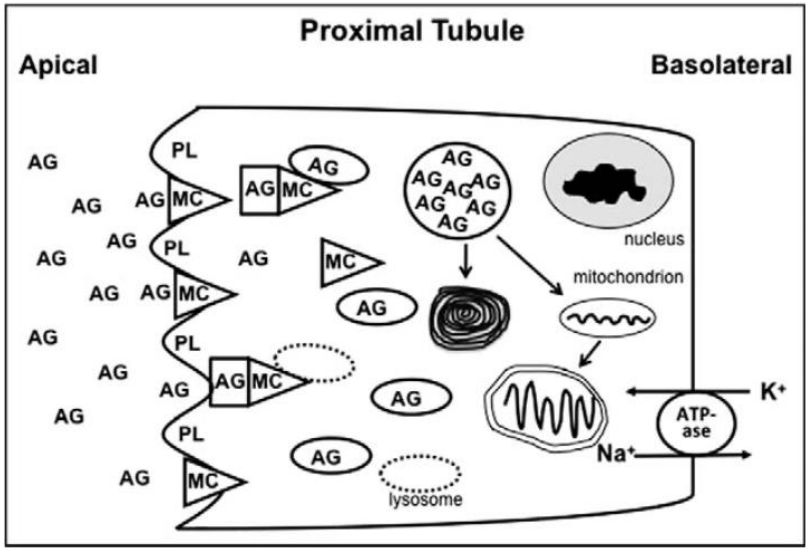
Fig. 4 (See legend on next page.)

Tsutsuura et al. BMC Infectious Diseases (2021) 21:153

Intra-Renal - ATN - Antibiotics

Aminoglycosides

- AKI occurs within 5-10 days of therapy initiation
- High drug concentration in proximal tubular epithelial cells leading to production of reactive oxygen species that produce mitochondrial injury, apoptosis and necrosis
- Toxicity related to cationic charge which facilitates binding to negatively charged renal tubular epithelial membrane phospholipids in the proximal tubules
- Most cationic → greater nephrotoxicity (neomycin, gentamicin, tobramycin, amikacin, streptomycin)



Curr Opin Crit Care 2019, 25:550 – 557

Intra-Renal - ATN - Antibiotics

Aminoglycosides

- Monitor trough level less than 2 mg/L
- Utilize alternate antibiotics 3rd generation 4th generation cephalosporines, fluoroquinolones
- Avoid volume depletion
- Avoid synergistic nephrotoxicity
- Maintain adequate hydration and hemodynamic stability

Intra-Renal AKI – ATN

Medication Class	Specific Medication	Preventative Strategies
Analgesics	NSAIDs & COX-2 inhibitors Acetaminophen overdose	Use alternative agents Avoid in high-risk patients Avoid excessive dosing (liver failure)
Chemotherapy agents	Cisplatin Ifosfamide Pemetrexed	Adjust dose for underlying eGFR IV isotonic-crystalloid-induced diuresis Use of lower-dose regimens Use of cisplatin analogs Limit Dose Mesna and N-acetylcysteine (unproven efficacy) Avoid in patients with eGFR < 45 ml/min
Radiocontrast agents	Iodinated radiocontrast agents	IV isotonic crystalloid hydration Low or iso-osmolar contrast agents
Calcineurin Inhibitors	Cyclosporine, tacrolimus	Reduce dose and follow drug levels Alternative agents (mTOR inhibitors)
Bisphosphonates	Pamidronate Zoledronic Acid	Increase infusion time (> 2 hrs) Use lower doses

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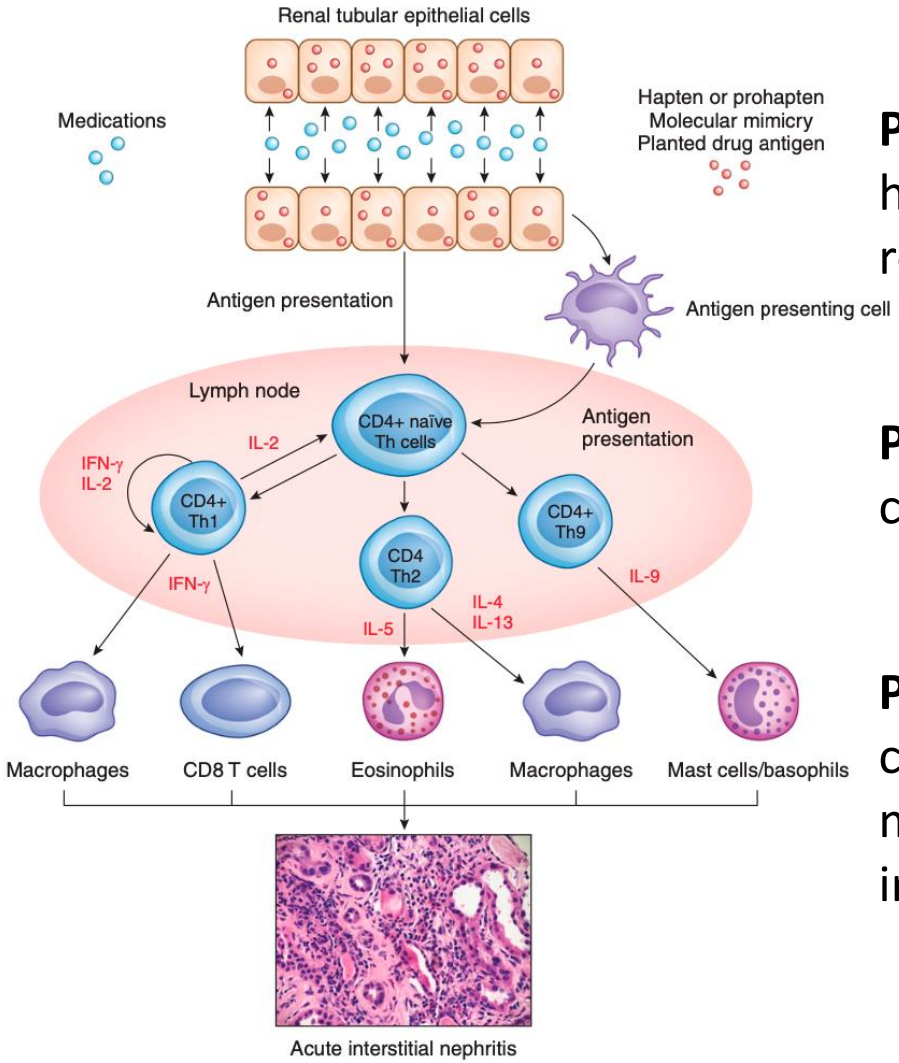
Intra-Renal AKI – Acute Interstitial Nephritis

- Immune mediated kidney injury characterized by infiltration of immune cells in the tubulointerstitium (commonly-T cell interstitial infiltrate)
- Drug induced AIN accounts for > 70% of AIN
- Observed in 10-27% kidney biopsies of hospitalized patients
- Dose independent and doesn't affect all patients
- Inconsistent presentation of rash, fever, eosinophilia/eosinophiluria with AKI only seen in 10-30% of patients
- Hypersensitivity reaction expected to recur with rechallenge
- Can cause permanent kidney damage from ongoing tubulointerstitial inflammation and fibrosis formation

Intra-Renal AKI – Acute Interstitial Nephritis



Phase 1: drug or metabolite act as hapten or prohapten which bind with renal proteins to form neoantigens

Phase 2: antigen is presented to T-cells

Phase 3: interstitial infiltration by T-cells, macrophages, eosinophils and mast cells which cause inflammatory infiltration in the interstitium

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Intra-Renal AKI – Acute Interstitial Nephritis

Medication Class	Individual Medications
Antibiotics	B-Lactam Drugs (Penicillin and derivatives, cephalosporins) Sulfa-base antimicrobials (trimethoprim-sulfamethoxazole, sulfadiazine) Fluoroquinolones Macrolides Rifampin
Antacid GI drugs	Proton pump inhibitors (class effect) Histamine-2 Blockers
Analgesics	NSAID including COX-2 inhibitors
Diuretics	Loop Diuretics (furosemide, bumetanide) Thiazide diuretics
Antiviral agents	Acyclovir, indinavir, atazanavir, foscarnet
Anticonvulsants	Phenobarbital, carbamazepine, phenytoin
Immunotherapies	PD-1 Inhibitors (nivolumab, pembrolizumab, cemiplimab) PD-L1 inhibitors (atezolizumab, durvalumab avelumab) CTLA-4 inhibitors (ipilimumab, tremelimumab)
Antiangiogenesis drugs	Bevacizumab, tyrosine kinase inhibitors (sorafenib, sunitinib)
Other agents	Ifosfamide, pemetrexed, lithium, allopurinol, mesalamine and other 5 -amino salicylates

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Intra-Renal AKI – Acute Interstitial Nephritis

- B-Lactam drugs
  - Presents approximately 14 days after initiation of therapy
  - Less prevalent than PPI induced AIN but more severe
  - Re-exposure to another class of B-Lactam is often tolerated suggesting absence of cross reactivity

- NSAIDs
  - Presents several months after initiation

- Proton Pump Inhibitors
  - Latent period of exposure to AIN is weeks to months
  - More common in older patients

Intra-Renal AKI – Acute Interstitial Nephritis

- Immune checkpoint inhibitors (ICPi)
  - Monoclonal antibodies that target immune pathways including CTLA-4, PD-1 and PD ligand-1 that dampen T cell activation/prevent autoimmunity and stimulate T-cell response against cancer cells
  - Risk Factors: low eGFR, concomitant PPI
  - Presents ~16 weeks after ICPi initiation
  - Renal recovery in 2/3 patients treated with corticosteroids
  - 16.5% rechallenged developed recurrent ICPi-AKI

Journal for ImmunoTherapy of Cancer 2021;e00346

Intra-Renal AKI – Acute Interstitial Nephritis

Management

- Discontinue suspected culprit
- Consideration of kidney biopsy
- Glucocorticoid therapy
  - Prednisone 1 mg/kg x 4-6 weeks

Table 5. Corticosteroid therapy in acute interstitial nephritis

Author, Year	Sample Size		Peak sCr (mg/dl) or eGFR (ml/min per 1.73 m^2)		Final sCr (mg/dl) or eGFR (ml/min per 1.73 m^2)		Follow-Up (months)	Study Details
	CS	No CS	CS	No CS	CS	No CS		
Clarkson *et al.* 2004 (89)	26	16	7.9	6.1	1.6	1.6	12	Patients received CS late after diagnosis (median delay >3 wk)
Gonzalez *et al.* 2008 (85)	52	9	5.9	4.9	2.1	3.7	19	CS-treated patients with complete recovery had shorter delay to CS (13 d) as compared with those without complete recovery (34 d)
Raza *et al.* 2012 (84)	37	12	6.5	5.2	2.8	3.4	19	Improved GFR with CS versus control ($P<0.05$). No difference in kidney outcomes on the basis of CS timing
Muriithi *et al.* 2014 (73)	83	12	3.0	4.5	1.4	1.5	6	CS-treated patients had superior kidney outcomes with early versus late CS therapy
Valluri *et al.* 2015 (87)	73	51	4.03	3.16	NR	NR	12	Worse kidney function in CS-treated versus control at biopsy (sCr 4.2 versus 3.3 mg/dl). CS-treated patients had complete recovery (48%) versus control group (41%); final sCr not different at 1 yr
Prendecki *et al.* 2016 (86)	158	29	eGFR 20.5	eGFR 25	eGFR 43	eGFR 24	24	CS-treated patient had better eGFR at 2 yr and less dialysis (5.1% versus 24.1%). Dose, duration, and time to CS initiation were variable
Yun *et al.* 2019 (88)	82	20	4.67	4.43	NR	NR	33 (median)	Kidney recovery at 6 mo: CS 58.5% versus 50% (NS); kidney recovery at last F/U: CS 78% versus 65% (NS); kidney failure: CS 14.6% versus 20% (NS)

CS, corticosteroids; NR, not reported; sCr, serum creatinine concentration; NS, not significant; F/U, follow-up.

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Post Renal – Drug-induced crystalline nephropathies

- Intratubular crystal deposition due to kidney route of drug/metabolite excretion and enhanced drug supersaturation within urine
- Supersaturation of crystal-forming drugs occurs with
  - volume depletion/dehydration (↓ urinary flow)
  - excessive drug dosing (↑ urinary drug concentration)
  - Urine pH depending on pK of drug

	Urine pH < 5.5	Urine pH > 6
Tubular obstruction by crystals and casts containing drugs and their metabolites	**Sulfadiazine Methotrexate Triamterene vancomycin**	**Indinavir Atazanir ciprofloxacin**

- Identification through Urine microscopy, kidney biopsy

Post Renal – Drug-induced crystalline nephropathies

- Crystalline related AKI caused by
  - Tubular obstruction
  - Crystal-related cytotoxicity and inflammation
    - Crystals promulgate intracellular signaling pathways and induce necrosis
- Prevention (see chart)
  - Appropriate drug dosing for level of GFR
  - Correct underlying volume depletion
  - Achieve high urinary flow rates
  - Target urine pH when applicable to prevent intratubular crystal precipitation

Post Renal – Drug-induced crystalline nephropathies

Culprit Medication	Clinical Kidney Syndromes	Preventive and Therapeutic Strategies
Methotrexate	Crystalluria, AKI, and CKD	IVFs, before/during drug, alkalinize urine, adjust drug dose for kidney function; folinic acid; glucarbidase (< 60 hr after MT); high-flux HD
Sulfadiazine, sulfamethoxazole	Crystalluria, AKI, and CKD, and nephrolithiasis	Alkalinize urine, adjust dose for kidney function, assure euvolemia before drug exposure
Indinavir, atazanavir, darunavir	Crystalluria, AKI, and CKD, and nephrolithiasis	No role for urine acidification, assure euvolemia during drug therapy; switch alternate agent
Acyclovir	Crystalluria, AKI, and CKD	Avoid rapid IV bolus, adjust dose for kidney function, assure euvolemia during drug therapy
Ciprofloxacin, levofloxacin	Crystalluria and AKI	Assure euvolemia during drug therapy and avoid alkaline urine (if possible)
IV ascorbic acid, orlistat, ethylene glycol	Crystalluria, AKI and CKD	Ascorbic acid and orlistat: assure euvolemia, avoid other nephrotoxins, fomepizole and HD for ethylene glycol
Sodium phosphate purgative (PO over enema)	AKI and CKD	Assure euvolemia, avoid NSAIDs, diuretics and RAS blockers
Triamterene	Crystalluria, AKI, CKD and nephrolithiasis	Alkalinize urine, assure euvolemia during drug therapy
Amoxicillin	Crystalluria and AKI	Assure euvolemia, adjust drug dose for kidney function
Foscarnet	AKI, hematuria, proteinuria and CKD	Assure euvolemia during drug therapy and adjust drug dose for kidney function

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Question

57 year old female one month post liver transplant taking sulfamethoxazole/trimethoprim DS 1 tablet 3 x weekly. Labs SCr 119 mmol/L (91 mmol/L), Urea 5 mmol/L (6 mmol/L), urine output unchanged.

This patient is likely experiencing AKI secondary to Septra

A) True

B) False

Pseudo-Nephrotoxicity

- Competition with creatinine for tubular secretion by drugs can mimic renal failure by increasing serum creatinine
- Medication-related serum creatinine increases are generally limited and return to baseline immediately following drug discontinuation
- Trimethoprim therapy can raise SCr from baseline by 17.6-31.3% with approximately 20% decrease in CrCl but GFR does not decrease due to pseudo elevation in in SCR.

J Infect Chemother 27 (2021) 1193e1197

Pseudo-Nephrotoxicity

Medications Associated with Pseudo-AKI	Mechanism of Increased Serum Creatinine
Cimetidine Trimethoprim Dronedarone Cobicistat and dolutegravir Tyrosine Kinase inhibitors (imatinib, bosutinib, sorafenib, sunitinib, crizotinib, gefitinib, pazopanib Pyrimethamine	Decrease creatinine secretion through the proximal tubular cells into the urine
Dexamethasone	Some formulations contain creatinine as an excipient
Cefoxitin	Recognized as a creatinine chromagen by the alkaline picrate method of creatinine analysis
Flucytosine	Interferes with enzymatic assay for serum creatinine determination
Corticosteroids	Catabolic state with release of creatine from muscle, which is converted to creatinine
Calcitriol and alfacalcidol	Unclear
Fenofibrate	Increase metabolic production of creatinine

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AKI – General Approach to Treatment

- Remove any nephrotoxic agents (where possible)
- **Prerenal AKI**: manage with hemodynamic support and volume replacement
- **Postrenal AKI**: remove cause of obstruction (where possible)
- AIN consider early steroids
- Use drug specific treatments
- Hemodialysis for toxic clearances
- Consider baseline kidney function
- Most effective treatment may be managing the comorbid precipitating event i.e. if the patient has sepsis, treat the sepsis!

How to Prevent AKI

- Be aware of risk factors:
  - Patient Related (age, sex, CKD, DM, etc)
  - Drug Related (dose, duration, frequency, infusion duration, MIC for antibiotics)
- Avoid Nephrotoxic Drugs
  - Renally dose adjust
  - Hold nephrotoxic drugs (RAASi, NSAIDs, diuretics, etc)
- Monitor
  - SCr, urine output, electrolytes, metabolic complications
  - Therapeutic drug monitoring
- Maintain
  - Blood pressure, euglycemia
- Educate
  - Sick day management of medications (SADMANS)

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