DRUG-INDUCED AKI

GENERAL RULES TO PREVENT AKI

1. Use the least nephrotoxic drug possible
2. Use the lowest effective dose of a drug
3. Avoid combination that has synergistic nephrotoxicity (ex// NSAIDs + ACEI)
4. Where applicable, adjust dose for kidney fxn
5. If a nephrotoxic drug is used:
    a. Ensure adequate hydration before & during therapy
    b. Expose the pt to the drug for as short as possible
    c. Be vigilant (is SCr: BUN ratio < 12?)

GENERAL RULES TO MANAGE ACUTE DIN

1. Discontinue nephrotoxic drug if possible (weigh pros and cons)
2. Ensure pt is adequately hydrated
3. Ensure appropriate monitoring (SCr, BUN, U/O)
4. Supportive RRT or removal of nephrotoxic drug

ALTERED INTRAGLOMERULAR HEMODYNAMICS: pre-renal DIN

Drugs	MOA	AKI prevention tips	AKI management tips
ACEI/ARBs	Inhibit ATII production = vasodilate efferent arteriole	• Check SCr 1-2 wks after initiation, then repeat in 2-4 weeks • Accept a 20-30% rise in SCr within 2 months of initiation	
NSAIDs	Anti-prostaglandin activity = vasoconstrict afferent artery	• Use alternative analgesia, especially in patients with CKD stage 3+ or in pts with decreased IVF	
Calcineurin inhibitors (cyclosporine, tacrolimus)	Dose-dependent vasoconstriction of afferent arterioles	• Monitor serum drug concentration (up to 2-3x during first week) • Monitor SCr and BUN (accept 30% rise in SCr) • Watch for drug interactions that will increase calcineurin inhibitors	• Try reducing the dose before considering D/C • In kidney transplant pts, differentiate between CNI-induced renal dysfunction and acute rejection

ACUTE INTERSITIAL NEPHRITIS: unusual allergic response to a drug (not dose-dependent)

- **Classic triad**: eosinophilia (>75%), fever, rash (50%)
- **Onset**: 2 weeks after drug exposure, 3-5 days if previously sensitized
- **Drugs**: allopurinol, antibiotics (**b-lactams**, cephalosporins, tetracyclines, quinolones, **rifampin**, sulfonamides, vancomycin), antivirals (acyclovir, indinavir), diuretics (loop, thiazides), **NSAIDs,** phenytoin, **PPIs**, H_2Ras
- **Management**: immediately discontinue offending agent; if no significant improvement w/in 3-7 days initiate prednisone 1mg/kg/day (max 60 mg) x minimum 1-2 weeks, tapered for duration of 2-3 months

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ACUTE TUBULAR NECROSIS: aminoglycosides, amphotericin B, contrast dye, antiretrovirals (adefovir, cidofovir, tenofovir), cisplatin, foscarnet, vancomycin, zoledronic acid

> Direct tubular toxicity (impair mitochondrial fxn, interfere with tubular transport, increase oxidative stress, form free radicals, cause heme tubular toxicity, abnormal phospholipid metabolism)

Drugs	MOA	AKI prevention tips

Aminoglycosides	• Bind to megalin (receptor transporter)
	• Taken into proximal tubular cells (10-100x higher concentrations)
	• Interfere with protein synthesis → ATN
	• Neomycin > gentamycin, tobramycin > amikacin, streptomycin
	  ○ Related to cationic charge
	• Clinical presentation:
	  ○ Gradual ↑ SCr after 5-10 days
	  ○ Generally non-oliguric (> 500 mL/day)
		• Use extended interval dosing where possible (not in enterococcus endocarditis)
		• Monitor serum drug levels if extended interval dosing used for > 48h or if multiple daily dosing used for > 24 h
		  ○ Extended dosing: trough target is undetectable
		  ○ Multiple dosing: trough target depends on AMG & indication
		• Limit duration of therapy (<10 days) and avoid repeated courses if possible
		• Administer during active periods of the day (chronotherapy)

Amphotericin B	• Direct tubular epithelial cell damage by binding to cell wall and increasing tubular permeability and necrosis • Incidence 80% when cumulative dose of 2g is reached	• Monitor SCr, BUN, lytes q1-2 days • Use liposomal formulation → enhances delivery to fungi instead of other cholesterol containing cells (like kidney)
Vancomycin	• Damage to proximal tubules through oxidative stress • Dose-dependent effect suggested	• Monitor SCr weekly • Monitor trough levels and adjust dose when required ○ Take levels when: deteriorating or unstable renal function, obese (BMI > 40), anticipated therapy > 7 days, severely ill, require trough of 15-20, altered Vd (children, elderly, burn pts), select dialysis pts

Contrast dye	• Increased oxygen consumption & decreased RBF lead to renal medullary hypoxia
	• Also causes direct cellular toxicity
	• Risks: pre-existing renal insufficiency, heart failure, diuretics, volume depletion, > 75 years old, high/frequent dosing, diabetes, NSAIDs, multiple myeloma, high osmolar/ionic agents, CKD
		• Minimize dose of contrast and avoid closely spaced repition
		• Use low or iso-osmolar agents
		• Avoid volume depletion and NSAIDs
		• Give IV hydration (better than PO)
		  ○ NS IV 1 mL/kg/h x 12 h pre and post
		  ○ $NaHCO_3$ IV 150 mEq/L D5W 3 mL/kg/h x 1 hr pre, then 1 mL/kg/h x 6h post

OBSTRUCTIVE NEPHROPATHY: antibiotics (ampicillin, ciprofloxacin, sulfonamides); antivirals (acyclovir, foscarnet, ganciclovir, indinavir, tenofovir); methotrexate; triamterene

> **Risk factors:** dehydration & CKD
> **Presentation:** often asymptomatic; renal colic symptoms (flank/abd pain, NV); urinalysis (hematuria, pyuria, crystalluria)
> **Pathogenesis:** direct (precipitation of drug or metabolites in urine); indirect (promoting precipitation of degradation products or cellular casts)

Drugs	MOA	AKI prevention tips	AKI management tips
Acyclovir	• Rapidly cleared from plasma, high concentrations in distal tubular lumen cause crystallizations (highly insoluble in urine pH) • Risk greater w/ IV but can happen with PO • Rapid rise in SCr in 12-48h	• Avoid rapid bolus infusions (max infusion rate 1h for every 500 mg) • Adequate **hydration with NS** to induce U/O of 100- 500 mL/hr • Dose adjust for pre-existing renal failure	• Introduction of diuresis with **furosemide** to wash out obstructing crystals (recommended if fluid overloaded) • **Hemodialysis** for acyclovir removal in SEVERE cases (neurotoxicity)
Methotrexate	• MTX and metabolites precipitate in renal-tubules (dose-dependent, often in high-dose continuous infusions) • Non-oliguric presentation • Usually reversible	• **Hydration:** maintain U/O of 100-200 mL/h x 24 h post high dose • Urinary alkalization: 75 mEq of **Na bicarb** per liter of NS IV at 125 mL/hr starting 12 h before and continued for 24-48h after MTX	• Urinary alkalization: 100-150 mEq of **Na bicarb** per liter of D5W IV at 125-150 mL/h until MTX level <0.05 • **Leucovorin rescue** (especially if >500 mg/m^2 was given) to treat bone marrow toxicity • **Glucarpidase** (inactivates extracellular MTX) 50 units/kg IV over 5 mins
Ciprofloxacin	• Insoluble in alkaline or neutral pH • Oliguric, usually within 2-14 days	• Avoid alkalizing urine	
Oral sodium phosphate purgatives	• Transient hyperphosphatemia → increased precipitation of CaPO4 in distal tubule • Increases in SCr but asymptomatic (days – months later)	• Poor prognosis (complete recovery is rare) • Avoid in renal dysfunction, elderly, volume depletion, ACEI/ARB users	
Anticoagulant-related nephropathy	Glomerular hemorrhage with intratubular obstruction by RBC casts		Restoration of INR to therapeutic range

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RHABDOMYOLYSIS:

- Skeletal muscle injury → lysis of myocyte → release of myoglobin (directly toxic to renal tubules & obstructive) and creatinine kinase
- **> 150 drugs** implicated (drugs of abuse, statins)
- **Management**
  - Hydration: maintain U/O of 200-300 mL/h until myoglobinuria stops & CK <5000 units/L
    - If CK < 5000, IV fluid not required
  - Hyper K, PO4, urea & hypo Ca management

GLOMERULONEPHRITIS:

- Immune mechanisms → inflammation → fibrosis & renal scarring
- **Drugs:** lithium, **gold**, interferon-alfa, **NSAIDs**, penicillamine, heroin, hydralazine, captopril, propylthiouracil, pamidronate, zoledronate
- **Management:**
  1. Discontinue drug & optimize conservative therapy
  2. If:
     a. Membranous nephropathy: consider immunosuppression after 6-12 months if no recovery
     b. Minimal change disease: corticosteroid x 3-4 weeks

THROMBOTIC MICROANGIOPATHY (TMA):

	Toxicity mediated	Immune mediated
Pathogenesis: kidney damage caused by platelet thrombi in afferent arteriole and glomerulus	Direct endothelial toxicity and activation of platelet aggregation	Formation of autoantibodies to metallo-proteinase that cleaves vWF → activation and adhesion of platelet
Drugs	Calcineurin inhibitors (cyclosporine, tacrolimus), mitomycin C, gemcitabine, bleomycin, cisplatinum, daunorubicin, vincristine, estrogen-containing OCs, cocaine;	
	Quinine	Ticlopidine, clopidogrel
Presentation: macroangiopathic, hemolytic anemia, thrombocytopenia, AKI	Gradual onset over weeks to months of weakness, fatigues, headaches, progressive kidney injury	Sudden onset of severe systemic symptoms (chills, fevers, GI, anuria, neurological changes) in 2-3 wks of drug exposure
Management: discontinue offending drug and provide spportive care	Quinine-induced: warn patients that even low concentrations of quinine in beverages (tonic water) can cause recurrent, severe episodes	• Implicated drug must be avoided for life as subsequent exposures can be severe and even fatal
Role of PLEX (plasma exchange):	• First line for ticlopidine • Optimum role not established for clopidogrel, calcineurin inhibitors • NOT RECOMMENDED (ineffective, harmful) for gemcitabine or quinine	

DRUG-INDUCED AKI

CHRONIC KIDNEY DISEASE aka medication-related chronic interstitial nephritis

> Slow progressive elevation of creatinine with or without tubular dysfunction syndromes (renal tubular acidosis, K wasting, concentration defects)

> **Drugs: chronic analgesic use** (ASA, NSAIDs, acetaminophen), **lithium,** cisplatin, cyclosporine, Chinese herbs (aristocholic acid)

ANALGESIC NEPHROPATHY

> Toxic metabolites of various analgesics build up in renal medulla due to countercurrent mechanism

> Leads to vasoconstriction, ischemic injury, cortical atrophy and eventually interstitial changes

> **Clinical pearls**:

- Difficult to diagnose and controversy exists (risk, prevention, cause?)
  - Commonly seen in females in 60s and 70s with chronic pain syndromes (headaches, joint, back)
- Use analgesics for SHORTEST duration possible
  - CHRONIC use should be under supervision of a physician to monitor kidney function
  - Caused by ingestion of 1 g of analgesics per day for > 20 years
- NO RISK from regular use of low-dose ASA for CV prevention
- Acetaminophen = analgesic of choice in patients with underlying kidney disease
  - AVOID COMBO products (acetaminophen with ASA or caffeine)

> **Management:** D/C analgesia and monitor for gross hematuria (as there's increased risk of uroepithelial tumors)

LITHIUM NEPHROPATHY:

> Nephrogenic diabetes insipidus: lithium enters collecting tubule via sodium channels and interferes with ADH's ability to increase water reabsorption; also reduces expression of aquaporins in collecting tubules

> Chronic interstitial nephritis: as a result of long-term exposure causing interstitial fibrosis and CKD

> **Clinical pearls:**

- Positive correlation with duration of treatment and impairment of urinary concentration ability (6.5-10 yrs)
- Dose reduce or D/C drug with elevations in SCr
  - If SCr > 220 umol/L at presentation, patient is likely to progress to ESRD despite D/C of lithium