

# Drug-Induced Acute Renal Dysfunction

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## Outline

- Pseudo Renal Failure
- Acute Renal Failure
  - Prerenal
    - NSAIDs, CyA/Tacrolimus, ACEI/ARB, Diuretics
  - Intrinsic – ATN vs AIN
    - ATN – Aminoglycosides, Amphotericin B, Radiocontrast Media
  - Obstructive
    - Methotrexate, Acyclovir, Indinavir, Rhabdomyolysis (Statins)

## Pseudo Renal Failure

- ↑ **BUN** due to protein catabolism
  - Steroids, tetracyclines
- ↑ **SCr** due to competitive inhibition of creatinine secretion
  - Trimethoprim, Cimetidine, Triamterene
  - Trimethoprim
    - 15-35% rise SCr fully expressed after 3 days
    - More sig in pts with pre-existing renal dysfunction
    - Can occur with normal doses
    - Completely reversible when drug is discontinued

(J Int Med 1999;246:247-52; TDM 1987;9:161-5)

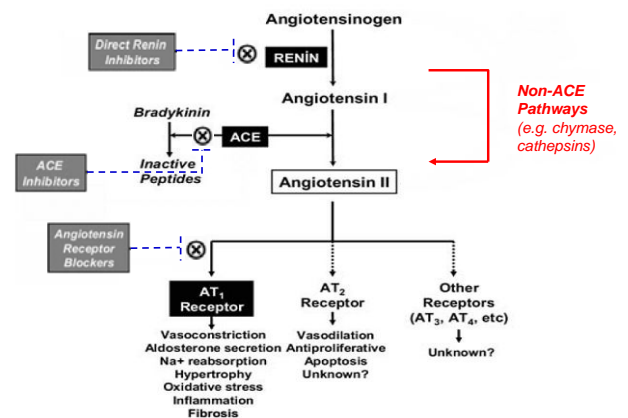
## Acute Renal Failure: PRE-RENAL

- ACEI/ARB
- NSAIDs
- Diuretics
- Immunosuppressives (CyA, Tacrolimus)

## Case: ACEI and Renal Failure

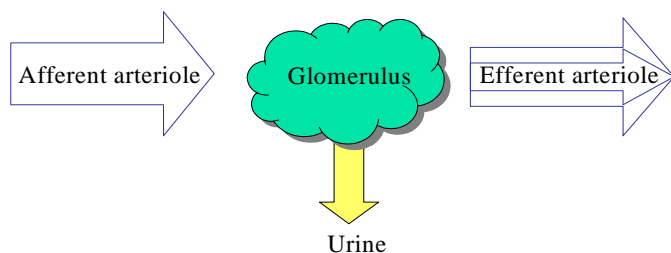
- Case 1: 52 yo male with Type 2 DM
  - baseline creatinine 159umol/L; BP 148/92
  - Ramipril 5 mg daily started and 2 weeks later:
    - BP 138/82
    - Serum creatinine 194umol/L
- Case 2: 82 yo female with osteoarthritis
  - Admitted to hospital for CAP & dehydration
  - Meds: Losartan 100mg daily + Naproxen 250mg BID
  - Serum creatinine 250 umol/L

## ACEI/ARB Pathway



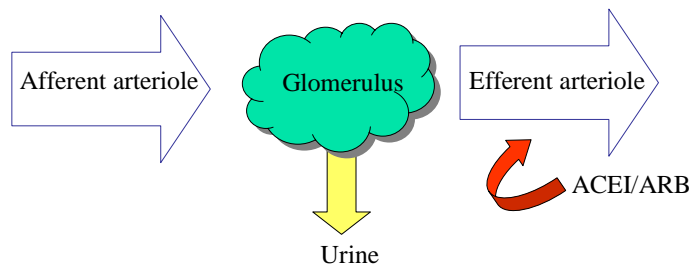
## ACEI/ARB and the Kidney

Angiotensin II  
vasoconstricts  
efferent arteriole



↑ Glomerular Capillary Pressure → ↑ Permeability → ↑ Proteinuria

## Renal Protective Properties of ACEI/ARB



Benefits of ACEI/ARB: decreased intraglomerular pressure and reduction of proteinuria

## Pathogenesis of ARF with ACEI/ARB

### Afferent Arteriolar Vasoconstrictors:

Vasodilatory PG Inhibitors: NSAIDs

Direct Afferent Vasoconstrictors:

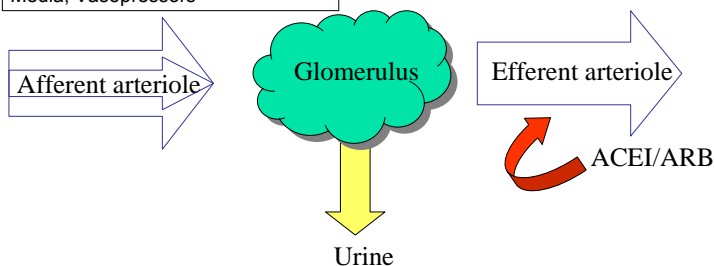
CyA, Tacrolimus, Radiocontrast Media, Vasopressors

### Efferent Arteriolar Vasodilators:

RAAS: ACEI, ARB

Direct Efferent Vasodilators:

Diltiazem, Verapamil



Renal function becomes dependent on sustained constriction of efferent arteriole from angiotensin II

## Risk Factors for ARF with ACEI/ARB

- Decreased intravascular volume (dehydration, diuretic overuse, CHF, vomiting, diarrhea)
- Use of afferent vasoconstrictor agents (NSAIDs, cyclosporine, tacrolimus)
- Sepsis
- Renal-artery stenosis
- Polycystic kidney disease

## Optimal Use of ACEI/ARB

(NEJM 2002;347:1256-61, Arch Int Med 2000;160:685-93)

### Case 1: Creatinine ↑ 159 to 194 in 2 weeks

- accept 20-30% increase in serum creatinine within 1-2 months of initiation
  - in fact, this could be an indication that the drugs are exerting their desired actions to help preserve renal function
  - check serum creatinine 1-2 weeks after initiation, then in 2-4 weeks
  - if > 30% change, decrease ACEI/ARB dose by 50% and repeat Ser Cr in 4 weeks (exclude hypovolemia/NSAIDs, etc)
  - if > 50% rise in Ser Cr – rule out RAS
- repeat serum creatinine in this patient in 1-2 weeks to ensure it has stabilized

## Optimal Use of ACEI/ARB

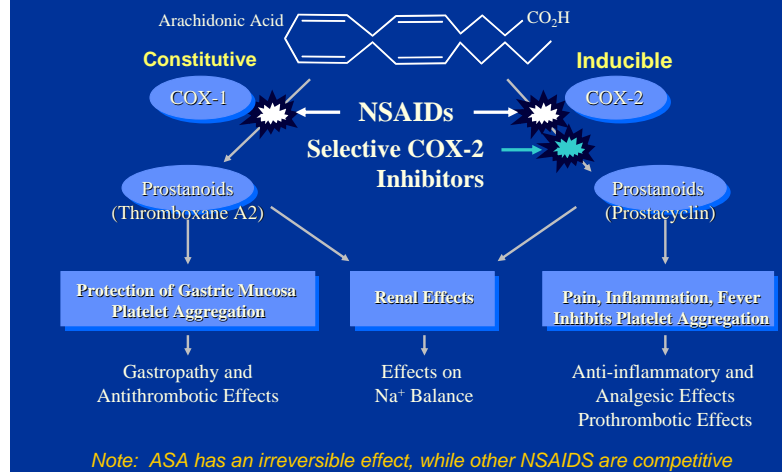
### Case 2: Creatinine on admission 250 umol/L in patient with CAP and dehydration

- discontinue NSAID and hold ARB until infection treated and patient is rehydrated/creatinine reduced
- resume ARB and monitor serum creatinine

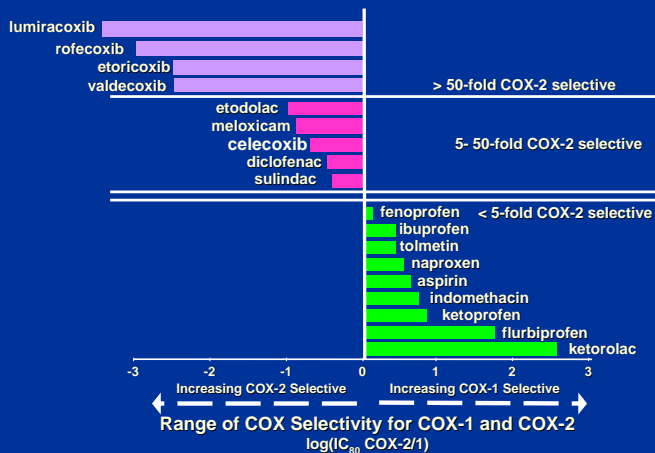
## NSAIDs/COX II Inhibitors

- **Case # 2:**
  - Physician would like to switch previous patient from Naproxen to Celecoxib
- Are Cox II inhibitors less likely to cause acute renal failure compared to NSAIDs?

## COX-1 and COX-2 Hypothesis (1992)



## In Vitro Selectivity: COX-2/COX-1 Ratio



Adapted from: Warner *et al.* *FASEB J.* 2004;18:790-804

## NSAIDs/COXibs

- Use with caution in CKD (grade 3 or greater)
- Inhibit renal vasodilatory prostaglandins E2 & I2
  - **Produced by COX-2**
- Reversible reduction in GFR
  - Higher risk if intravascular volume depletion
  - Management: D/C drug, use alternate analgesia
- Hypertension
  - Edema, sodium and water retention
  - Mean increase SBP 5 mm Hg
- Hyperkalemia Risk
  - blunting of PG-mediated renin release

## Cyclosporine, Tacrolimus

- Can cause pre-renal (hemodynamically mediated) or chronic interstitial nephritis
- Pre-renal – dose-related
  - preglomerular arteriolar vasoconstriction or direct proximal tubule damage
  - ↑ SCr ~ 30%
  - More common in first 6 mos of therapy
  - Hypertension, ↑ K, ↓ Mg may occur
  - Reversible with lowering dose (caution rejection)
  - Monitor blood levels
  - Renal biopsy to distinguish acute CyA nephrotoxicity from allograft rejection

## Acute Renal Failure: INTRINSIC

Acute Interstitial Nephritis (AIN) vs  
Acute Tubular Necrosis (ATN)

	AIN	ATN
<b>Onset</b>	1 <sup>st</sup> exposure: > 10-14days* 2 <sup>nd</sup> exposure: 3-5 days	Early (7-10 days)
<b>Clinical Features</b>	Classic Triad: Fever, Rash (50%), eosinophilia (> 75%)*	Uremic Symptoms
<b>Urinalysis</b>	WBC casts, eosinophiluria, hematuria, mild proteinuria*, oliguria	Granular casts, renal epithelial casts; oliguria, ↑F <sub>e</sub> Na
<b>Diganosis</b>	Renal biopsy – gold standard	History, exam, lab, urine
<b>Time Course</b>	RF should begin to recover ~7d; May have residual CKD 36-40%	Usually reversible and GFR return to BL in 7-14d
<b>Treatment</b>	D/C offending agent (not dose-related); if persists: Prednisone**	D/C offending agent (can be dose-related)
<b>Common Drugs</b>	Anti-Infectives: Beta-lactam, Sulfa, Rifampin, Ciprofloxacin; Other: NSAIDs, PPI, Cimetidine, Allopurinol, Phenytoin, Diuretics	Anti-infectives: A/G, Vanco, AmphoB, Sulfa; Contrast Media, Cisplatin

\*NSAIDs - onset 2-3mos; no eosinophilia/uria, fever or rash; proteinuria > 3g/24h;  
\*\*Reserve if delayed renal recovery (> 1 wk), prolonged exposure to agent (> 2-3 wks)

## ATN: Aminoglycosides

- Incidence 5-20%
- Onset
  - Gradual ↑ SCr after 5-10 days
- Pathogenesis
  - Tubular epithelial cell damage leading to obstruction of tubular lumen
- Presentation
  - Non-oliguria > 500mL/day; granular casts in urine
- Risk Factors
  - Combination therapy with other nephrotoxic drugs
  - Total cumulative dose; trough levels > 2 mg/L; repeated courses of A/G therapy; prolonged therapy > 10 days
  - Dehydration
- Management – Reversible if D/C drug, adequate hydration, monitor levels

## ATN: Aminoglycosides

- Is once daily dosing less nephrotoxic compared to traditional dosing?

## Once Daily A/G Dosing: 4.5-6 mg/kg Q24H (eGFR ≥ 60 mL/min)

- Theory why once daily A/G therapy works:
  - Concentration-dependent kill (10x MIC)
  - Post-antibiotic effect
- Exclusion
  - Burns > 20%, Septic Shock, Synergy
  - GFR < 60 mL/min, Dialysis
- Potential for reduced nephrotoxicity
  - Proximal tubular A/G uptake appears to be limited during transient, high-peak serum levels
  - Low A/G concs for a greater proportion of dosing interval facilitate excretion of A/G
- Nephrotoxicity
  - Only 1/4 meta-analyses showed reduced nephrotoxicity (from 7.7% to 5.5%); rest showed **no difference**

## ATN: Amphotericin B

- Incidence: ~80% when cumulative dose reaches 2 g
- Pathogenesis
  - Direct tubular epithelial cell damage; binds to cell wall resulting in ↑ tubular permeability and necrosis
- Presentation
  - ↑ SCr, BUN, ↓ Mg, K (urinary wasting) – monitor q1-2d
  - Distal RTA, polyuria (nephrogenic DI)
- Risk Factors
  - Combination therapy with other nephrotoxic drugs
  - Total cumulative dose; daily dose > 0.5mg/kg/day
  - Dehydration
- Management – Reversible if D/C drug, Hydration (1L NS daily)

## ATN: Amphotericin B

- Are Liposomal formulations less nephrotoxic compared to traditional Amphotericin B deoxycholate?

## Liposomal Amphotericin B

- Theory for reduced nephrotoxicity
  - Reduced nephrotoxicity by enhancing the delivery to sites of infection, thus reducing exposure to mammalian cell membranes
  - Cochrane review April 2000 – all lipid-based preps **decreased the occurrence of nephrotoxicity**
  - AKI still occurs, esp if concurrent exposure to other nephrotoxic drugs
- Amphotericin B deoxycholate vs Liposomal
  - VGH guidelines: only prescribe Ampho B if GFR > 50mL/min and low risk for renal failure
  - Drawback Liposomal - **Very expensive** (\$440-735/day)

## Alternatives to Liposomal Ampho

- Invasive aspergillosis
  - **Voriconazole** (~\$100 PO; ~\$400 IV)
  - Cannot use IV voriconazole if GFR < 50 mL/min due to accumulation of vehicle
  - CYP2C9 and 3A4 inhibitor (↑ CyA, Methadone, statins, tacrolimus, vincristine, warfarin)
- Invasive candidiasis
  - **Fluconazole** – 1<sup>st</sup> line for uncomplicated pts (\$20/day)
    - CYP 2C9 inhibitor (↑ warfarin, phenytoin)
  - **Echinocandin** (micafungin -\$50/day) for complicated pts (neutropenic, unknown Candida isolates, hemodynamically unstable, recent azoles)
    - may ↑ CyA, sirolimus

## ATN: Radiographic Contrast Media

- Incidence: 40-50% in high risk pts (CKD, DM)
- Onset: within 12-24 hrs, SCr peaks 2-5 days after exposure, recovery usually after 4-10 days
- Pathogenesis
  - Direct tubular necrosis, renal ischemia
- Presentation
  - Typically non-oliguric (high risk may require HD)
  - Urinalysis – hyaline and granular casts, low F<sub>E</sub>Na
- Risk Factors: DM, CKD, prestudy dehydration
- Management – Low-osmolality nonionic contrast agents (eg. Iohexol), smallest dose, Hydration

## Interventions to Prevent Contrast Nephrotoxicity

- **Which is best proven prevention strategy?**
  - NS 1-2 mL/kg/hr starting 12 hours pre and continued 12 hours post-procedure
  - Sodium Bicarbonate 150mEq/L D5W infused at 3mL/kg/h x 1 hours pre, then 1mL/kg/h x 6 hours post-procedure
  - N-acetylcysteine 600mg PO BID x 4 doses on day prior to and on day after admin of contrast

## Recommended Interventions for Prevention of Contrast Nephrotoxicity

(DiPiro Pharmacotherapy 2009)

Intervention	Recommendation	Grade <sup>a</sup>
<b>Contrast</b>	■ Minimize contrast volume/dose	A-1
	■ Use noniodinated contrast studies	A-2
	■ Use low-osmololar contrast agent	A-2
<b>Medications</b>	■ Avoid concurrent use of potentially nephrotoxic drugs (e.g. NSAIDs, A/G)	A-2
<b>Normal Saline</b>	1mL/kg/h up to 150mL/h pre and post contrast exposure	A-1
<b>Sodium Bicarbonate 150 mEq/L D5W</b>	3mL/kg/h 1 hour prior to contrast exposure, then 1mL/kg/h for 6 hours post contrast	B-2 (JAMA 2004)
<b>Acetylcysteine</b>	600mg PO BID x 4 doses pre and post	B-1

<sup>a</sup>Strength of Recommendation A, B, C (Good, Moderate, Poor)

Quality of Evidence: 1 (R, Controlled), 2 (R, Cohort), 3 (Expert opinion)

## Acute Renal Failure: Obstructive Nephropathy

- Statins: Rhabdomyolysis, Tumor Lysis Syndrome
- Crystalluria: Methotrexate, Sulphonamides, Acyclovir, Indinavir

## ARF: Obstructive Nephropathy

- **Rhabdomyolysis**
  - Intratubular precipitation of myoglobin
  - Reddish-brown urine
  - Statins: simvastatin, atorvastatin – risk ↑'ed with Cyp 3A4 inhibitors (clarithromycin, erythro, itraconazole) or combination fibrate
- **Prevention**
  - **Hold Statin** while on clarithro/erythro or itraconazole therapy (alternative azithromycin OK)
  - Pravastatin, Rosuvastatin not metabolized by CYP 3A4

## Drug-Induced Crystalluria

- Drug insoluble in urine and crystallizes in distal tubule
- Risk Factors:
  - Decreased circulating volume
    - High concentration of drug in tubular fluid
    - Prolonged intratubular transit time
  - Renal dysfunction
    - ↑ amount of drug excreted per functioning nephron
  - Acid or alkaline urine pH
- Prevention:
  - Dosage adjustment for underlying renal failure
  - Volume expansion to enhance urinary output
  - Urinary alkalization (for weak acids)
- Full Renal Recovery expected

## ARF: Drug-Induced Crystalluria

(Drug insoluble in urine and crystallizes in distal tubule)

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>■ <b>Methotrexate</b> <ul style="list-style-type: none"> <li>■ Weak Acid – precipitates in acidic urine (pH &lt; 7)</li> <li>■ Precipitation of MTX and its metabolite in renal tubules</li> <li>■ High dose MTX (12-15g/m<sup>2</sup>)</li> </ul> </li> <li>■ <b>Prevention</b> <ul style="list-style-type: none"> <li>■ Diuresis – U/O 100-200mL/h x 24h post-high dose MTX</li> <li>■ Urinary alkalization (sodium bicarb 25-50 mEq/L hydration fluid)</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>■ <b>Acyclovir</b> <ul style="list-style-type: none"> <li>■ Weak acid and weak base</li> <li>■ Intratubular precipitation of acyclovir in dehydrated oliguric patients</li> <li>■ Needle-shaped crystals</li> </ul> </li> <li>■ <b>Risks/Prevention</b> <ul style="list-style-type: none"> <li>■ IV – too fast infusion rate               <ul style="list-style-type: none"> <li>■ Infuse over 1 hour</li> </ul> </li> <li>■ High dose &gt; 500mg/m<sup>2</sup></li> <li>■ Dehydration – IV NS</li> <li>■ Pre-existing renal failure – adjust dose</li> <li>■ Other nephrotoxins</li> </ul> </li> </ul> |
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## ARF: Drug-Induced Crystalluria

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>■ <b>Indinavir</b> <ul style="list-style-type: none"> <li>■ Protease inhibitor for HIV</li> <li>■ Weak base - precipitates in alkaline urine</li> <li>■ Crystal nephropathy (8%) dysuria, urinary freq</li> <li>■ Rectangular crystals</li> </ul> </li> <li>■ <b>Risk/Prevention</b> <ul style="list-style-type: none"> <li>■ Severe volume depletion</li> <li>■ Precipitation prevented by consumption of ~2 L fluid per day</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>■ <b>Sulphonamides</b> <ul style="list-style-type: none"> <li>■ Weak Acid – precipitates in acidic urine</li> <li>■ Higher doses</li> <li>■ More common with sulfadiazine</li> </ul> </li> <li>■ <b>Risk/Prevention</b> <ul style="list-style-type: none"> <li>■ Volume depletion - maintain good fluid intake</li> <li>■ Renal dysfunction - adjust dose</li> <li>■ Urinary alkalization (treatment)</li> </ul> </li> </ul> |
|---|---|

## Tips: Reducing Drug-Induced Toxicities

<b>Opioids</b>	<p><b>Meperidine</b> metabolite (normeperidine) is neurotoxic and may cause seizures – C/I GFR &lt; 50 mL/min</p> <p><b>Fentanyl and Methadone</b> preferred for chronic pain management as no active metabolites</p> <p><b>Hydromorphone</b> preferred over Morphine (less 3-glucuronide metabolite - myoclonus, hallucinations)</p>
<b>NSAIDs</b>	Caution if GFR < 30-60 mL/minute → ARF, ↑ K, hypertension esp if patient on ACEI or diuretics
<b>Sulfonylureas</b>	<p><b>Chlorpropamide</b> –↑'ed half-life, prolongs hypoglycemia</p> <p><b>Glyburide</b> has active metabolite - ↑ t1/2 → hypoglycemia</p> <p><b>Gliclazide</b> preferred agent – no active metabolite (needs SA) (glyburide 5mg = gliclazide 80mg = gliclazide MR 30mg)</p>
<b>Metformin</b>	Do not use if GFR < 30-60 mL/min → lactic acidosis
<b>Insulin</b>	↓ renal clearance – potential for hypoglycemia
<b>Allopurinol</b>	Dosage adjustment; 100mg/day max in Stage 5 (dialysis)

## References

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