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


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

Non-ACE Pathways (e.g. chymase, cathepsins)
ACEI/ARB and the Kidney

- Angiotensin II vasoconstricts efferent arteriole

Afferent arteriole → Glomerulus → Efferent arteriole → Urine

↑ 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


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

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?

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

- Lumiracoxib: > 50-fold COX-2 selective
- Rofecoxib: > 50-fold COX-2 selective
- Etoricoxib: > 50-fold COX-2 selective
- Valdecoxib: > 50-fold COX-2 selective
- Etodolac: > 50-fold COX-2 selective
- Meloxicam: > 50-fold COX-2 selective
- Celecoxib: > 50-fold COX-2 selective
- Diclofenac: > 50-fold COX-2 selective
- Sulindac: > 50-fold COX-2 selective
- Naproxen: > 50-fold COX-2 selective
- Ibuprofen: > 50-fold COX-2 selective
- Aspirin: > 50-fold COX-2 selective
- Indomethacin: > 50-fold COX-2 selective
- Ketoprofen: > 50-fold COX-2 selective
- Fenoprofen: > 50-fold COX-2 selective
- Flurbiprofen: > 50-fold COX-2 selective
- Ketorolac: > 50-fold COX-2 selective

**NSAI Ds/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

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**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

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**Acute Renal Failure:**

**INTRINSIC**

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

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 update 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)

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 FENa
- 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 (DiPro Pharmacotherapy 2009)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
<th>Gradea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast</td>
<td>Minimize contrast volume/dose</td>
<td>A-1</td>
</tr>
<tr>
<td></td>
<td>Use noniodinated contrast studies</td>
<td>A-2</td>
</tr>
<tr>
<td></td>
<td>Use low-osmolar contrast agent</td>
<td>A-2</td>
</tr>
<tr>
<td>Medications</td>
<td>Avoid concurrent use of potentially nephrotoxic drugs</td>
<td>A-2</td>
</tr>
<tr>
<td>Normal Saline</td>
<td>1mL/kg/h up to 150mL/h pre and post contrast exposure</td>
<td>A-1</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>3mL/kg/h 1 hour prior to contrast exposure, then 1mL/kg/h for 6 hours post contrast</td>
<td>B-2</td>
</tr>
<tr>
<td></td>
<td>150 mEq/L D5W</td>
<td>(JAMA 2004)</td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td>600mg PO BID x 4 doses pre and post</td>
<td>B-1</td>
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aStrength of Recommendation A, B, C (Good, Moderate, Poor)
Quality of Evidence: 1 (R, Controlled), 2 (R, Cohort), 3 (Expert opinion)

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 – 1st 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

Acute Renal Failure: Obstructive Nephropathy

- Statins: Rhabdomyolysis, Tumor Lysis Syndrome
- Crystalluria: Methotrexate, Sulfonamides, Acyclovir, Indinavir
ARF: Obstructive Nephropathy

- Rhabdomyolysis
  - Intratubular precipitation of myoglobin
  - Reddish-brown urine
  - Statins: simvastatin, atorvastatin – risk ↑ with CYP 3A4 inhibitors (clarithromycin, erythromycin, 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 alkalinization (for weak acids)
  - Full Renal Recovery expected

ARF: Drug-Induced Crystalluria (Drug insoluble in urine and crystallizes in distal tubule)

- Methotrexate
  - Weak Acid – precipitates in acidic urine (pH < 7)
  - Precipitation of MTX and its metabolite in renal tubules
  - High dose MTX (12-15g/m²)

- Prevention
  - Diuresis – U/O 100-200mL/h x 24h post-high dose MTX
  - Urinary alkalinization (sodium bicarb 25-50 mEq/L hydration fluid)

- Acyclovir
  - Weak acid and weak base
  - Intratubular precipitation of acyclovir in dehydrated oliguric patients
  - Needle-shaped crystals

- Risks/Prevention
  - IV – too fast infusion rate
  - Infuse over 1 hour
  - High dose > 500mg/m²
  - Dehydration – IV NS
  - Pre-existing renal failure – adjust dose
  - Other nephrotoxins

- Indinavir
  - Protease inhibitor for HIV
  - Weak base - precipitates in alkaline urine
  - Crystal nephropathy (8%) dysuria, urinary freq
  - Rectangular crystals

- Risks/Prevention
  - Severe volume depletion
  - Precipitation prevented by consumption of ~2 L fluid per day

- Sulphonamides
  - Weak Acid – precipitates in acidic urine
  - Higher doses
  - More common with sulfadiazine

- Risk/Prevention
  - Volume depletion - maintain good fluid intake
  - Renal dysfunction - adjust dose
  - Urinary alkalinization (treatment)

Tips: Reducing Drug-Induced Toxicities

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