**A3. PHARMACISTS**

**DRUG-INDUCED KIDNEY INJURY**

2:00 - 3:00PM

**ACPE UAN:** 107-000-14-027-L01-P  
**Activity Type:** Application-Based  
0.1 CEU/1.0 hr

**Learning Objectives for Pharmacists:** Upon completion of this CPE activity participants should be able to:
1. Describe the basic pathophysiology of drug induced kidney injury
2. Identify risk factors for drug induced kidney injury
3. Review drugs associated with renal disease, in particular to the mechanism of inducing injury and clinical presentation
4. Develop a systematic approach to determine the classification of kidney injury & likely cause
5. Describe preventive measures and outline a management plan in the setting of drug induced kidney injury

**Speaker:** Brett Heintz, PharmD, BCPS-ID, AAHIVE, received his doctorate in pharmacy from the University of California, San Francisco and completed his residencies in pharmacy practice and infectious diseases at the University of California, Davis Medical Center in Sacramento, CA. He also is a board certified pharmacotherapy specialist with added qualifications in infectious diseases and American Academy of HIV expert certified.

Dr. Heintz, a Pharmacy Specialist in Internal Medicine and Infectious Diseases, joined the Iowa City VA Health Care System in September 2012. He also holds an academic position as Associate Clinical Professor at the University of Iowa College of Pharmacy and precepts pharmacy students, delivers didactic lectures and coordinates a pharmacotherapy course. Prior to joining the Iowa City VA and the University of Iowa he served as an Assistant Professor of Clinical Pharmacy at UC San Francisco School of Pharmacy with a clinical practice in Infectious Diseases and Internal Medicine at UC Davis Medical Center.

Dr. Heintz's primary research and clinical interests include antimicrobial dosing in special populations, including renal failure, dialysis, hepatic failure and obesity; determination of predictors of resistance, treatment failure and toxicity of antistaphylococcal and antipseudomonal agents; and management of outpatient delivery of antimicrobial therapy.

Dr. Heintz has authored several articles and book chapters related to antimicrobial therapy and has presented his many of his research projects at local, state, national, and international level meetings. He is also the recipient of several teaching awards.

**Speaker Disclosure:** Brett Heintz reports no actual or potential conflicts of interest in relation to this CPE activity. Off-label use of medications will be discussed during this presentation.
Drug-Induced Kidney Injury

Brett Heintz, BS, PharmD, BCPS (AQ-ID), AAHIVE
Associate Professor (Clinical)
University Of Iowa College of Pharmacy
Clinical Pharmacy Specialist
Iowa City VA Health Care System
Medicine/Infectious Diseases


Faculty Disclosure

• No actual or potential conflicts of interest associated with this presentation

• Off-label use of medications will be discussed during this presentation
Learning Objectives

Upon completion of this activity, pharmacists should be able to:

1. Review drug induced kidney injury pathophysiology
2. Identify risk factors for drug induced kidney injury
3. Review drugs associated with kidney injury, mechanism of inducing injury & clinical presentation
4. Develop a systematic approach to determine the classification of kidney injury & likely cause
5. Provide preventative measures & management plan in the setting of drug induced kidney injury

Drug Induced Kidney Disease: Epidemiology

- 5-10% of drug toxicities involve kidney injury
  - Drug induced kidney disease is common in hospitals
- Kidney at risk because:
  - High exposure to toxins, high energy requirement
  - Intra-renal metabolism, autoregulation, etc.
- Mechanisms of drug induced AKI:*
  - Alterations in renal perfusion or filtration capacity
  - Direct Damage: vascular, tubular, glomerular, interstitial cells

*AKI = acute kidney injury: ≥ 1.5-fold increase in baseline SCr OR UOP < 0.5mL/kg/hr x 6 hours
Drug Induced Kidney Disease: Risk Factors

- **Demographics**
  - Age > 70 years
  - Gender: female
  - Race: African American
- **Pre-existing kidney dz**
- **Other comorbidities**
  - Diabetes
  - Heart Failure & cirrhosis
    - Cardiorenal / Hepatorenal
- **Allergies**
- **Pharmacogenomics**
  - Renal Transporters
  - Cyp P450 enzyme
- **Volume depletion**
  - Sepsis/Shock
  - Surgery
  - Dehydration
  - Acid/base disorder
- **Other nephrotoxins**
  - Exposure: dose/duration


Drug Induced Kidney Disease: Manifestations

- **Acid-base abnormalities**
- **Electrolyte abnormalities**
- **Increase in blood urea nitrogen (BUN)**
- **Increase in serum creatinine (SCr)**
- **Urinalysis (UA) abnormalities**
  - Urine sediment abnormalities
  - Proteinuria (protein in urine)
  - Pyuria (pus or white blood cells in urine)
  - Hematuria (blood in urine)

Classifications of Acute Kidney Injury

**Acute Kidney Injury**

1. **Prerenal**
   - Include any condition that reduces blood flow to kidney (ischemia)

2. **Intrinsic / Intrarenal**
   - Glomerulovascular or tubulointerstitial

3. **Postrenal**
   - Result from obstruction of urine flow from the kidney to the ureters & bladder

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### Urinary Indices in AKI (Reference)

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Prerenal</th>
<th>Intra-renal</th>
<th>Post-renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na\textsubscript{urine} (mEq/L)</td>
<td>20 – 40</td>
<td>&lt; 20 (low)</td>
<td>&gt;20 (usually high)</td>
<td>&gt;40 (high)</td>
</tr>
<tr>
<td>FE\textsubscript{Na} (%)</td>
<td>~1</td>
<td>&lt;1 (low)</td>
<td>&gt;1 (high)</td>
<td>Variable</td>
</tr>
<tr>
<td>FE\textsubscript{Urea}</td>
<td>40-50%</td>
<td>&lt; 35%</td>
<td>&gt;50%</td>
<td>Variable</td>
</tr>
<tr>
<td>BUN:SCr ratio</td>
<td>10:1</td>
<td>&gt;20:1 (high)</td>
<td>15:1</td>
<td>15:1</td>
</tr>
<tr>
<td>Ucr:SCr ratio</td>
<td>20-40</td>
<td>&gt;40:1 (high)</td>
<td>&lt;20:1 (low)</td>
<td>&lt;20:1 (low)</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/kg)</td>
<td>300 – 500</td>
<td>&gt; 500 (high)</td>
<td>&lt; 300 (low)</td>
<td>&lt; 300 (low)</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.010 – 1.020</td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>None</td>
<td>Normal, may have hyaline casts</td>
<td>Granular casts, epithelial cells, debris</td>
<td>Urate/phosphate crystals, myoglobin, may be normal</td>
</tr>
<tr>
<td>WBC and RBC</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Variable</td>
</tr>
<tr>
<td>Protein</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Etiology

- Pre-renal ischemia
- Intrinsic renal disease
  - Acute Interstitial Nephritis
  - Acute Tubular Necrosis
- Post-renal obstruction

Pre-Renal Ischemia

- The healthy kidney receives 25% of cardiac output
  - Oxygen extracted for secretion and reabsorptive functions
- Kidney susceptible to reduced blood flow (ischemia)
  - Vasoconstriction of afferent arterioles: ↓ intraglomerular pressure
  - Vasodilation of efferent arterioles: ↓ renal perfusion
- Occurs more often in patients who can’t compensate for alterations in afferent/efferent blood flow
  - Elderly & volume depleted
  - Heart failure (cardiorenal)
  - Liver failure (hepatorenal)

### Causes of Decreased Oxygen Delivery

- **Volume depletion**
  - Absolute (dehydration) vs. functional (ascites, CHF)
- **Vasoconstriction of the medulla**
  - Endothelin, AT-II
- **Disruption in Tubuloglomerular Feedback (TGF)**
- **Thrombosis**
  - Decreased blood flow
- **Pre-existing kidney disease**
- **Medullary workload**
  - Active transport primary determinant of O2 consumption

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### Offending Agents & Risk Factors

<table>
<thead>
<tr>
<th>Offending Agents</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constrict Afferent</td>
<td>Volume depletion</td>
</tr>
<tr>
<td>- NSAIDs / COX 2-Inhib.</td>
<td>- Dehydration</td>
</tr>
<tr>
<td>- Calcineurin inhibitors</td>
<td>- Diuretic overuse</td>
</tr>
<tr>
<td>- Cyclosporine</td>
<td>- Functional (CHF, ascites)</td>
</tr>
<tr>
<td>- Tacrolimus</td>
<td>- Sepsis (blood shunting)</td>
</tr>
<tr>
<td>- Radiocontrast Media</td>
<td>- Vomiting / Diarrhea</td>
</tr>
<tr>
<td>Dilate Efferent</td>
<td>Renal-artery stenosis</td>
</tr>
<tr>
<td>- ACEI, ARB, hydralazine</td>
<td>Polycystic kidney disease</td>
</tr>
<tr>
<td>- Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>- Diuretics</td>
<td></td>
</tr>
</tbody>
</table>

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NSAIDs / Calineurin-I & ACE-Inhibitors Induced Kidney Injury

- NSAIDs/COX-2-I
  - Prostaglandin Inhibition
    - Results in vasoconstriction of the afferent arteriole
- Other offending agents
  - cyclosporine, tacrolimus
  - Radiocontrast dye

- ACE-I / ARB
  - Angiotensin Inhibition
    - Results in vasodilation of the efferent arteriole
- Other offending agents
  - CCBs, hydralazine
  - Diuretics


Drug Induced Pre-Renal Ischemia: Presentation: Urinalysis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Urinalysis (UA)</th>
<th>BUN/SCr</th>
<th>Urine to Plasma Osmolality</th>
<th>UNa</th>
<th>Fractional excretion of Na^o</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td>Normal, ± hyaline casts</td>
<td>&gt;20</td>
<td>&gt;1</td>
<td>&lt;20</td>
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<td>Interstitial nephritis</td>
<td>+ eosinophils, RBC, WBC, ± granular casts</td>
<td>≤15</td>
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<td>RBC, RBC casts, proteinuria</td>
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<td>Vascular disorders</td>
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<tr>
<td>Postrenal</td>
<td>Normal or RBC, WBC, crystal</td>
<td>≤15</td>
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^ FENa (%) = Urine Na * Plasma Cr * 100
FENa=Fractional Excretion of Na; Na= Sodium; Cr= Creatinine
FE Urea <35% is better predictor of pre-renal if receiving diuretics
Management

- Discontinue offending agent
  - Use safer alternatives

- Hydration
  - Crystalloids (0.9% normal saline) vs. colloids (albumin)
    - SAFE (Saline vs. Albumin for Fluid Evaluation) study
      - Outcome | Albumin | Saline | RRR (95% CI) | NNT
      - All cause mortality | 20.9% | 21.1% | 1% (-9 to 9) | Not significant
  - Cost
    - Albumin 20x more expensive than 0.9% normal saline


Etiology

- Pre-renal ischemia
- Intrinsic renal disease
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  - Acute Tubular Necrosis
- Post-renal obstruction
Acute Interstitial Nephritis (AIN)


Drug Induced AIN: Pathophysiology

- Inflammation of kidney interstitium & tubules
- Infiltration of the interstitial compartment by inflammatory/immune cells
  - T-cells, monocytes, plasma cells, eosinophils
- Immune complex reaction or cell mediated response to offending drugs
- Diagnosis made by renal biopsy
### Drug Induced AIN: Offending Agents

- Allopurinol
- NSAIDs
- Phenytoin
- Azathioprine
- Chinese Herbs
  - stephania tetrandra, magnolia officinalis, aristolochia fangchi
- Cimetidine (H2As)
- Omeprazole (PPIs)
- Diuretics (thiazides, loops)
- Gold
- Antibiotics
  - **Semisynthetic penicillins**
    - nafcillin, oxacillin, piperacillin
  - **Sulfonamides**
  - **Vancomycin**
  - Quinolones
  - Rifamycins
  - Macrolides

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### Drug Induced AIN: Presentation (Signs & Symptoms)

- Onset is variable (days to weeks)
  - Generally **subacute picture** (> 7-10 days)
- Acute kidney injury with or without oliguria
  - Generally mild increase in SCr and mild reduction in UOP
- Urinalysis
  - RBCs, WBCs, ± WBC casts, ± proteinuria (see next slide)
  - + **Eosinophils** (peripheral eosinophilia as well)
- Tubular dysfunction
  - polyuria, vol. depletion, hyperkalemia, metabolic acidosis
- Other
  - urticarial rash, fever, myalgias, **evidence on renal biopsy**
Drug Induced AIN:
Presentation: Urinalysis*

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* Specificity high (>75%): if + can rule-in AIN, however sensitivity is poor (<50%): if – cannot rule-out AIN


AIN: Prognosis & Treatment

- Usually reversible after discontinuation of the offending agent
- Use of corticosteroids are controversial
  - No clear benefit in literature
  - Possible benefit in the setting of prolonged oliguria
    - Prednisone 1mg/kg/day for ≥ 3 days then consider taper

**AIN: Treatment (Supplemental)**

Patient with renal insufficiency, AIN suspected (subacute, mild oliguria, eosinophils)

- Withdraw potential agent

  - Improved renal function
  - No clinical improvement

- Observe, supportive care
- Renal Biopsy or alternative study (calium 67 scan, ultrasound)

  - Positive
  - Evidence of severe fibrosis?
    - Yes
      - Continue supportive care and consider trial of (alternative) immunosuppressive therapy
    - No
      - Contraindication to corticosteroid
        - Yes
          - Contraindication to corticosteroid
        - No
          - No

  - Negative
    - Evaluate for other causes of renal failure


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**Etiology**

- Pre-renal ischemia
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Acute Tubular Necrosis (ATN)

Drug Induced ATN: Pathophysiology

- Direct renal tubular toxicity / acidosis
- Disruption of mitochondrial respiration
  - deranged cellular energy production
  - free radical injury: reactive oxygen species formation
- Cytosolic calcium overload
- Osmolar changes with vacuolization injury
- Damage correlated to total exposure: dose, duration
- Mechanism of toxicity is unique to each agent
Drug Induced ATN: Offending Agents

- **Contrast**
- **Aminoglycosides**
- **Amphotericin B**
- **Colistin**
- Cisplatin, carboplatin
- Cyclophosphamide, Ifosfamide
- Pentamidine
- Vancomycin (?)

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Drug Induced ATN: Presentation (Signs & Symptoms)

- **Onset is rapid (days)**
  - Generally considered to be *acute onset* (≤ 7-10 days)
- **Acute kidney injury with or without oliguria**
  - Generally rapid increase in SCr & decrease in UOP
  - Rise in SCr correlated with trough drug concentrations
- **Urinalysis**
  - Renal/granular casts, epithelial cells, necrotic cells
- **Tubular dysfunction / Electrolyte abnormalities**
  - hyperkalemia, hyperphosphatemia, metabolic acidosis
Drug Induced ATN: Presentation: Urinalysis*

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* Contrast nephropathy presents as pre-renal, then progresses to an intra-renal like presentation


Contrast Induced Nephrotoxicity

- Contrast media utilized to optimize visualization of blood flow
  - Varying osmolality in relation to plasma
    - Iohexal
    - higher osmolar agent
    - Iodixanol
    - lower osmolar agent
  - Lower osmolar agents & dose reduce risk for AKI
- Effects on kidneys
  - Reactive oxygen species & high osmotic load
    - Direct tubular toxicity
  - Systemic hypotension, volume depletion, vasoconstriction (↓ nitric oxide)
    - ↓ kidney blood flow
  - Blocks autoregulation of medullary blood flow

Contrast Induced Nephrotoxicity: 
Presentation

- Pre-renal picture with superimposed intra-renal injury
  - Transient osmotic diuresis, then direct tubular toxicity (ATN)
- Abrupt increase in SCr
  - SCr rises/peaks in 2-5 days
- Marked reduction in UOP
  - 50% patients develop oliguria (UOP < 400mL/24h)
- Urinalysis findings (see Tables)
  - Early: consistent with pre-renal injury
  - Late: consistent with intra-renal injury

Contrast Induced Nephrotoxicity: 
Prognosis & Treatment

- Prognosis
  - Due to abrupt nature of damage & susceptibility of cells to ischemic death, the damage is often irreversible
  - Higher mortality than inflammatory damage or direct toxin damage: multiple mechanisms
- Treatment
  - Withdraw offending agent (may be temporary)
  - Fluid replacement if volume depleted

Contrast Induced Nephrotoxicity: Prevention

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
<th>Grade</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 (iodixanol)</td>
<td>A-2</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydration (NS)</td>
<td>• Avoid concurrent nephrotoxins</td>
<td>A-2</td>
</tr>
<tr>
<td></td>
<td>• 1mL/kg/h 6-12 hours pre and post exposure</td>
<td>A-1</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>• 3mL/kg/h 1 hour prior to contrast exposure,</td>
<td>B-2</td>
</tr>
<tr>
<td>150 mEq/L D5W</td>
<td>then 1mL/kg/h for 6 hours post contrast exposure</td>
<td>(JAMA 2004)</td>
</tr>
<tr>
<td>Acetylcysteine (Mucomyst®)</td>
<td>• 600mg PO twice daily x 4 doses</td>
<td>B-1</td>
</tr>
<tr>
<td>(day before and day of radiocontrast study)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascorbic Acid (Vit C)</td>
<td>• 3g prior to procedure, 2g post &amp; 2g next day</td>
<td>C-2</td>
</tr>
</tbody>
</table>

* Strength of Recommendation: A, B, C (Good, Moderate, Poor)
* Quality of Evidence: 1 (Randomized controlled), 2 (Randomized, Cohort), 3 (Expert opinion)


Contrast Induced Nephrotoxicity

Saline vs. Sodium bicarbonate

Aminoglycoside Induced ATN

Pathophysiology (several hypotheses)
- Intracellular accumulation within lysosomes interferes with cellular functions and leads to cell death
- AGs stimulate calcium-sensing receptor on apical membrane which causes cell signaling / cell death

Recommendations / Prevention
- Consider extended interval dosing (q24h), if appropriate
  - Increase efficacy
    - Concentration dependent kill, Post antibiotic effect
  - Decreased toxicity
    - Minimizes exposure of nephrons (t ½ = 2h) as uptake is saturable
- Diligent monitoring (SCr, urine output, electrolytes, levels)
- Use appropriate dose for shortest duration possible
- Explore alternative antimicrobials, if possible
Amphotericin B Induced ATN: Multifactorial Mechanism of Toxicity

- Constriction of the afferent arterioles leading to decreased glomerular filtration
- Direct damage of distal tubular membranes leading to wasting of Na⁺, K⁺, and Mg²⁺

Tubular-glomerular feedback: Further constriction of arterioles

Amphotericin B Induced ATN

- Recommendations / Prevention
  - Liposomal formulations are less nephrotoxic
  - Avoid concomitant nephrotoxins
  - Fluid/sodium loading: NS pre/post drug administration
  - Prolonged infusion rates – controversial
  - Consider alternative antifungal agents, if possible
  - Monitor kidney function / electrolytes (K⁺, Mg²⁺)
    - Scheduled & sliding scale potassium & magnesium orders
  - Stop offending agent if evidence of kidney injury

Etiology

- Pre-renal ischemia
- Intrinsic renal disease
  - Acute Interstitial Nephritis
  - Acute Tubular Necrosis
- Post-renal obstruction

Obstructive Nephropathy
Obstructive Nephropathy

- Pathophysiology
  - Kidney tubular obstruction due to buildup of tissue degradation products
    - Drugs or other sediment precipitate within renal tubules
      - crystal or stone
  - Examples
    - Crystal induced nephropathy
    - Uric acid precipitation after tumor lysis
    - Myoglobin precipitation secondary to rhabdomyolysis

- Offending Agents
  - Cystalluria
    - Acyclovir
    - Allopurinol
    - Indinavir, Nelfinavir
    - Methotrexate
    - Sulfonamides
    - Triamterene
  - Rhabdomyolisis
    - Statins
    - Quinolones
    - Daptomycin

- Presentation
  - Timing is variable
  - Mild ↑ SCr
  - Mild ↓ UOP
  - Urinalysis (next slide)
    - Crystals or stones
    - ± urinary sediment
      - (RBC, WBC, granular casts)
    - No eosinophils

Drug Induced Obstructive Nephropathy: Presentation: Urinalysis*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Urinalysis (UA)</th>
<th>BUN/SCr</th>
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<th>Fractional excretion of Na⁺</th>
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<tr>
<td>Prerenal</td>
<td>Normal, ± hyaline casts</td>
<td>&gt;20</td>
<td>&gt;1</td>
<td>&lt;20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>+ eosinophils, RBC, WBC, ± granular casts</td>
<td>≤15</td>
<td>≤1</td>
<td>&gt;20</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>Granular/renal casts, epithelial/necrotic cells</td>
<td>≤15</td>
<td>≤1</td>
<td>&gt;20</td>
<td>&gt; &gt; 1</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>RBC, RBC casts, proteinuria</td>
<td>≤15</td>
<td>&gt;1</td>
<td>&lt;20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vascular-Hypovolemia</td>
<td>Normal or RBC casts, proteinuria</td>
<td>≤15</td>
<td>&gt;1</td>
<td>&lt;20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Postrenal</td>
<td>Normal or RBC, WBC, ± granular casts</td>
<td>≤15</td>
<td>&lt;1</td>
<td>&gt;40</td>
<td>variable</td>
</tr>
</tbody>
</table>


Obstructive Nephropathy: Prognosis & Treatment

- Usually reversible after reducing the dose or discontinuation of offending agent
- **Hydration**
- **Hydration**
- **Hydration**
- Alkaline diuresis or acidify urine depending on the characteristics of the drug
  - Alkaline: Na bicarbonate, polycitra (Na/K citrate)
  - Acidify: acetazolamide

Other: Glomerular disease

- **Pathophysiology / Definitions**
  - Glomerulonephritis: inflammation of the glomerulus
  - Glomerulosclerosis: scarring of kidney blood vessels
  - Causes include diabetes, lupus, medications

- **Causative drugs**
  - NSAIDs, heroin, hydralazine, procainamide

- **Urinalysis (see next slide)**
  - Proteinuria is hallmark sign, ± RBC & RBC casts

---

### Glomerulonephritis

**Presentation: Urinalysis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Urinalysis (UA)</th>
<th>BUN/SCr</th>
<th>Urine to Plasma Osmolality</th>
<th>UNa</th>
<th>Fractional excretion of Na⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td>Normal, ± hyaline casts</td>
<td>&gt;20</td>
<td>&gt;1</td>
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</tr>
<tr>
<td>Glomerulonephritis</td>
<td>RBC, RBC casts, proteinuria</td>
<td>≤15</td>
<td>&gt;1</td>
<td>&lt;20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Normal or RBC, proteinuria</td>
<td>≤15</td>
<td>&gt;1</td>
<td>&lt;20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Postrenal</td>
<td>Normal or RBC, WBC, sediment: crystal, stones...</td>
<td>≤15</td>
<td>&lt;1</td>
<td>&gt;40</td>
<td>variable</td>
</tr>
</tbody>
</table>

---

Other: Fanconi’s Syndrome

- **Pathophysiology**
  - Direct damage to the proximal tubules of the kidney
  - glucose, proteins, uric acid, phosphate, bicarbonate are secreted in urine instead of being reabsorbed

- **Causative drugs**
  - Tenofovir, adefovir, didanosine, tetracyclines

- **Presentation and Urinalysis**
  - Chronic (months), polyuria, polydipsia, dehydration
  - Proteinuria, glycosuria, hypophosph, hypoK, acidosis

---

Pseudo-drug-induced nephropathy

- **Drugs that inhibit SCr excretion (“pseudoazotemia”)**
  - Trimethoprim; cimetidine; probenecid; cobicistat
  - K-sparing diuretics: amiloride, triamterene spironolactone
    - Note: expect 10–30% increase in SCr from baseline

- **Drugs that increase BUN (hypercatabolic effect)**
  - Corticosteroids; tetracycline

- **Drugs that interfere with SCr assay**
  - Cefoxitin; levo/methyldopa; flucytosine; ascorbic acid
Patient Assessment

Clinical History
- Age, Size, Allergies, Sex
  - IBW vs. ABW for obese
- Renal function
- Urinalysis
- Medical Conditions
  - Baseline kidney disease
  - Autoimmune diseases
  - Infection, sepsis, N/V/D
  - Cardiac / liver disease

Medication History
- Concurrent medications
  - Cyclosporine, tacrolimus
  - ACE-I, ARB with NSAIDs
  - Diuretics
  - Aminoglycosides
- Nephrotoxin History
  - Dose & frequency
  - Duration of therapy
  - Time course
## Review: Drug Induced Kidney Injury

<table>
<thead>
<tr>
<th>Pre-Renal (↓ Blood delivery)</th>
<th>AIN</th>
<th>ATN</th>
<th>Crystal Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Allopurinol</td>
<td>Aminoglycosides</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>ACE-I / ARB</td>
<td>Azathioprine</td>
<td>Amphotericin B</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>NSAIDS / COX-II inhibitors</td>
<td>β-lactams (nafcillin, pip)</td>
<td>Colistin</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Cyclosporine / Tacrolimus</td>
<td>Chinese herbs</td>
<td>Cicloplatin</td>
<td>Nefilnavir</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Diuretics (thiazide, loops)</td>
<td>Carboplatin</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Gold</td>
<td>Cyclophosphamide</td>
<td>Fluoroquinolines</td>
</tr>
<tr>
<td>Lithium</td>
<td>Fluoroquinolones</td>
<td>Ifosfaide</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Radiocantrast Media</td>
<td>H2As (cimetidine)</td>
<td>Pentamidine</td>
<td>Triamterene</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>Macrolides, Rifamycins</td>
<td>Radiocontrast</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Vancomycin?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPIs (omeprazole)</td>
<td>Sulfonamides</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Supplemental Slide: Site-specific Drug Induced Kidney Injury

#### Proximal tubules
- ABX: Aminoglycoside, Colistin, Amphotericin
- Antivirals: Foscarnet, Cidofovir, Adefovir, TdF
- IS: Cyclosporine, Tacrolimus (FK), Cicloplatin

#### Distal Tubules
- Amphotericin B
- IS: FK, CSA, sulfadiazine
- Lithium

#### Renal vessel
- NSAIDs (afferent)
- ACE-I (efferent)
- Cyclosporine (CSA)

#### Pappillae
- Phenacetin

#### Collecting Duct
- Amphotericin B
- Acyclovir
- Lithium

#### Glomeruli
- Interferon-α
- Gold
- Doxorubicin
- Penicillamine
- Pamidronate

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Pre-Renal</th>
<th>Acute Tubular Necrosis (ATN)</th>
<th>Acute Interstitial Nephritis (AIN)</th>
<th>Crystal-Induced Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia</td>
<td>Direct cellular toxicity or renal blood flow impairment</td>
<td>Immune reaction after binding to endogenous nephrotogenic antigen</td>
<td>Precipitation within the renal tubules (crystal or stones)</td>
<td></td>
</tr>
<tr>
<td>Timing</td>
<td>Acute (≤ 7 d)</td>
<td>Acute (≤ 7 days)</td>
<td>Subacute (&gt; 7 days)</td>
<td>Anytime</td>
</tr>
<tr>
<td>SCr, Urine output</td>
<td>↑↑↑, ↓↓↓</td>
<td>↑↑↑, ↓↓↓</td>
<td>↑↓↓, ↓↑↑</td>
<td>↑↓↓</td>
</tr>
<tr>
<td>Electrolyte changes</td>
<td>Variable</td>
<td>HyperPhos / kalemia</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Urinalysis/other:</td>
<td>Normal</td>
<td>casts, epithelial cells</td>
<td>eosinophils, fever/rash</td>
<td>Crystals</td>
</tr>
<tr>
<td>BUN/Scr, osmolality</td>
<td>↑ (≥ 20, &gt; 1)</td>
<td>↑ (≥ 15, ≥ 1)</td>
<td>↑ (≥ 20, &gt; 2)</td>
<td>↑ (≥ 15, &gt; 1)</td>
</tr>
<tr>
<td>UNa, FENA</td>
<td>↓ (&lt; 20, &lt; 1)</td>
<td>↓ (&lt; 20, &lt; 1)</td>
<td>↓ (&lt; 20, &lt; 1)</td>
<td>↓ (&lt; 20, &lt; 1)</td>
</tr>
<tr>
<td>Common Antimicrobials</td>
<td>---</td>
<td>AGs, colistin, AmB, cidofovir, foscarnet</td>
<td>β-lactams, sulfa, FQs, vancomycin, macrolide</td>
<td>Acyclovir, sulfonamides</td>
</tr>
<tr>
<td>Other drugs</td>
<td>ACE-I, NSAID, Contrast, CSA</td>
<td>Thiazides, tacrolimus, cyclosporine, contrast</td>
<td>NSAIDs, allopurinol, cimetidine, diuretics</td>
<td>NSAIDs, thiazides, PI, PHT, allopurinol</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Age, underlying kidney disease, volume depletion (CHF, ascites, etc.)</td>
<td>β-lactam / sulfa allergy</td>
<td>Rapid, high dose (IV), vol. depletion</td>
<td></td>
</tr>
</tbody>
</table>

**Systematic Review:**
Drug Induced Kidney Injury


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**Conclusions**

- Kidney injury has many implications in regards to drugs
  - Many drugs can result in kidney injury
  - Altered kidney function can affect excretion of many drugs
- Drug-induced kidney injury can be (sub)acute or chronic, and of prerenal, intrarenal, or postrenal mechanisms
- Renal injury caused by drugs can be minimized if detected early & preventative measures are utilized
  - Minimize dehydration and hypotension
- Appropriate monitoring & dose adjustments needed

* vascular, tubular, glomerular, interstitial
Key References


Case 1

CC/HPI

CC: Dizziness
HPI: GL is a 84 y/o & 62kg female with AMS who was brought to the ED by her daughter from her skilled nursing facility. She was discharged from the hospital 1 week ago following treatment for a CHF exacerbation. The patient is unable to provide a history at this time. According to the daughter, GL initially felt less fatigued and short of breath, which she attributes to the increased dose of her “water pill” that GL has continued to take since her hospital discharge. Her daughter, has noticed that GL has become progressively more confused and lethargic over the last few days. Today, the patient became very dizzy and lightheaded when trying to stand up and her daughter decided to bring her to the ED. GL also complains of tachypnea, fever & pleuritic chest pain, and in the ED the patient was found to have evidence of pneumonia.

PMH

CHF, DM, HTN, osteoarthritis, CKD, diabetic gastroparesis

Allergies

None

Medications

PTA: Lisinopril 20 mg po qday (started 1/1/2014), furosemide 80 mg po bid (increased 1/14/ 2014), metformin 500 mg po bid, sitagliptin 100 mg/d, glyburide 20mg/d, ibuprofen 200-400 mg po qid prn for pain (ave. 1200mg/day), MVI po qday, metoclopramide 10 mg po qid
On admit: cefepime 1g IV q12h, vancomycin 1g IV q24h, famotidine 20mg q24h, heparin 5000 U SC bid
Case 1 (cont)

**Urinalysis**

| Collection: clean catch | Bacteria: neg |
| Clarity: cloudy | Hyaline casts: positive |
| Color: yellow | Granular casts: negative |
| Specific gravity: 1.032 | Leukocytes esterase: negative |
| Glucose: neg | Nitrites: neg |
| Protein: 30 mg/dl | UNa 15 mEq/L |
| WBC: neg | Ucr 113 mg/dL |
| RBC: small | Uosm 614 mOsm/kg |
| Bacteria: neg | Hyaline casts: positive |
| Granular casts: negative | Leukocytes esterase: negative |
| Nitrites: neg | UNa 15 mEq/L |
| UNa 15 mEq/L | Ucr 113 mg/dL |
| Uosm 614 mOsm/kg | Uosm 614 mOsm/kg |

| Physical Exam | Labs |
| GENERAL: elderly female in no apparent distress | Na 137 mEq/L |
| SKIN: dry, no rashes | K 5.7 mEq/L |
| CHEST + crackles R lung base | Cl 101 mEq/L |
| CV: RRR | HCO3 28 mEq/L |
| ABD: no tenderness/distension | BUN 65 mg/dL |
| UOP: 300ml/24hours on day of admission | Scr 3.0 mg/dL |
| | Glu 72 mg/dL |
| | Ca 8.6 mg/dL |
| | Mg 2.1 mEq/L |
| | Phos 4.4 mg/dL |
| | Hgb 13.9 g/dL |
| | Hct 41.3% |
| | Plts 239K |
| | WBC 9.2K |
| | Alb 2.8 g/dL |

Case 1 (cont)

1. What risk factors does the patient have for her AKI?
2. What is the most likely etiology of her AKI?
   - Pre-renal, intrinsic (AIN / ATN) or post-renal?
3. What agent(s) is/are likely contributing to AKI?
4. Are any agents contraindicated in AKI?
   - Which agents should be used with caution in AKI?
5. Provide a management plan, including providing alternative therapy if needed for problematic agents.
Post-Assessment Questions

1. Risk factors for drug induced acute kidney injury include:
   A. Advanced age
   B. Pre-existing renal disease
   C. Diabetes
   D. All of the above

2. Which of the following statement(s) is/are consistent with drug-induced acute interstitial nephritis (AIN)?
   A. Timing consistent with acute onset (< 7 days)
   B. Fraction of excreted sodium (FENA) < 1%
   C. Evidence of eosinophils in the urinalysis
   D. ALL of the above

3. **True or False.** The MOST important treatment option when managing drug induced acute kidney injury is stopping the offending agent?

4. Which of the following statement(s) is/are consistent with drug-induced Acute Tubular Necrosis (ATN)?
   A. Timing consistent with acute onset (< 7 days)
   B. Fraction of excreted sodium (FENA) > 2%
   C. Evidence of renal casts in the urinalysis
   D. ALL of the above

5. JR is a 82 year old female with hypertension currently receiving lisinopril. JR’s PCP instructs JR to take ibuprofen to help manage some joint pain. **True or False.** The addition of an NSAID to a patient receiving an ACE-I may increase the risk for pre-renal ischemia and associated nephrotoxicity.

6. **True or False.** Use of acetylcysteine or sodium bicarbonate is the primary method to reduce the risk for post-renal (obstructive) nephropathy.
Questions