Drugs and Kidney: Clinical Pharmacology for The Nephrologist

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Focus of The Talk

- Introduction
- Pharmacokinetics
- Iatrogenic renal diseases
- Drugs acting on the kidney
- Special issues
- Conclusion
Renal Vulnerability to Drug Toxicity

Kidney Specific Factors

- High drug delivery: (RBF = 20-25% of cardiac output)
- High metabolic rates & workload of cells
- Cellular uptake of toxin
- ↑ Local drug concentration in medullary cells/interstitium
- Renal biotransformation of drugs: ↑ toxic metabolites & reactive intermediates

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  - Drugs acting on the kidney
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- Conclusion
Pharmacokinetics

- Bioavailability:
  - Furosemide dosing oral/IV

- Drug absorption
  - Gastric absorption
  - Phosphate binders
  - Antacids
  - Subcutaneous and intramuscular routes of absorption
  - Peritoneal absorption
Pharmacokinetics:
Drugs and Body Compartments

Absorption site → Drug in blood

- Drug in urine
- Metabolites
- Drug in stool

Drug in other fluids (CSF, lymph)
Drug in tissues (fat, skin, joint space)
Hydrophilic drugs:
- Decreased Vd in dehydration and increased Vd in edema

CKD affects Vd
- Digoxin

Protein binding
Pharmacokinetics

Distribution:
- Higher free fraction of drugs in plasma in uremia
- Lower concentrations of total drug
  - Lower therapeutic levels of Phenytoin
Pharmacokinetics:
Biotransformation or metabolism

- Biochemical conversion from one chemical form to another mediated by hepatic enzymatic pathways
- Pharmacologically active metabolites of inactive prodrugs that depend on renal excretion:
  - Lisinopril to lisinoprilat
  - Meperidine to normeperidine
- Downregulation of cytochrome P450 in CKD
A paucity of information exists regarding altered pharmacology in the critical care setting, where acute kidney failure, hepatic insufficiency, altered volume status, hypoalbuminemia, multiple drug interactions, and the use of various dialysis techniques further complicate drug-dosing regimens.
Drug Metabolism:

- Uremia affects drug metabolism and reduces non-renal clearance of drugs.

- First pass metabolism by the liver of some drugs such as Inderal or cimetidine may be reduced in renal impairment.
Renal drug excretion:

- It depends on
  - Filtration
  - Active tubular secretion/reabsorption
  - Passive diffusion.
- Drugs of MW < 60,000 Dalton are filtered through the glomerulus.
- Lipid soluble drugs that diffuse readily across tubular cells whereas water soluble compounds do not.
Factors That Affect Drugs Dialysis

Drug
- size (molecular weight)
- % protein bound
- volume of distribution
- water solubility (% of dose appearing “unchanged” in urine)

Membrane
- size (surface area)
- permeability (pore size)
- composition (polysulfone, cellulose-based, etc.)
- drug-membrane-binding characteristics (if any)

Dialysis method
- dialysis (drug removal by diffusion)
- hemofiltration (drug removal by convection)
- duration of procedure
- blood and dialysate flow rate
- ultrafiltration rate
- replacement solution location (pre- or postfilter)
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- **Iatrogenic renal diseases**
- Drugs acting on the kidney
- Special issues
- Conclusion
Acute Kidney Problems Caused by Nephrotoxins

- Prerenal azotemia
- Acute tubular necrosis
- Acute interstitial nephritis
- Acute glomerulonephritis
- Crystal nephropathy
- Obstructive nephropathy
- Renal tubular acidosis/Fanconi syndrome
- Sodium wasting (Bartter-like syndrome)
- Potassium wasting
- Distal renal tubular acidosis
- Nephrogenic diabetes insipidus
# Acute Kidney Problems Caused by Nephrotoxins

<table>
<thead>
<tr>
<th>Mechanism of toxicity</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>Penicillamine, gold</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Alteration in renal blood flow</td>
<td>RAAS inhibitors, NSAIDs</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Hydralazine, procainamide, isoniazid, propylthiouracil, phenytoin</td>
</tr>
<tr>
<td>Tubular toxicity (Fanconi’s syndrome or specific tubular deficits)</td>
<td>Ifosfamide, amphotericin</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Crystalluria (aciclovir, indinavir, methotrexate)</td>
</tr>
<tr>
<td></td>
<td>Sloughing of papillae (analgesics)</td>
</tr>
<tr>
<td></td>
<td>Retroperitoneal fibrosis (methysergide, bromocriptine)</td>
</tr>
</tbody>
</table>
# Tubulopathy Syndromes Induced by Antimicrobials

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
</table>
| Aminoglycosides and tetracyclines  
proximal RTA or Fanconi syndrome  
Bartter-like syndrome  
Amphotericin B compounds  
distal RTA (H⁺ “backleak”)  
hypokalemia  
polyuria/hyponatremia  
Trimethoprim  
distal RTA  
blockade of ENaC  
Penicillins  
hypokalemia  
hyperlalemia  
Linezolid and tetracyclines  
lactic acidosis | Normal anion gap metabolic acidosis; hypokalemia; uric acid, glucose, amino acid, phospho-wasting  
Metabolic alkalosis with K⁺, Ca⁺, Mg⁺, Na⁺ wasting  
Normal anion gap metabolic acidosis  
K⁺ wasting; distal RTA  
Nephrogenic diabetes insipidus  
Normal anion gap metabolic acidosis  
Hyperkalemia  
High urine K⁺, low urine Cl⁻  
High K⁺ content in setting of poor kaliuresis  
High anion gap metabolic acidosis |

ENaC, epithelial sodium channels; RTA, renal tubular acidosis.
Acute Renal Failure
Nephrotoxic ATN

- **Endogenous Toxins**
  - Heme pigments (myoglobin, hemoglobin)
  - Myeloma light chains

- **Exogenous Toxins**
  - Antibiotics (e.g., aminoglycosides, amphotericin B)
  - Radiocontrast agents
  - Heavy metals (e.g., cis-platinum, mercury)
  - Poisons (e.g., ethylene glycol)
Aminoglycoside Nephrotoxicity

- Nonoliguric acute renal failure
- Slow (4-6 wk) recovery of renal function
- Proximal tubule dysfunction (enzymuria, proteinuria, aminoaciduria, glucosuria)
- Hypomagnesemia
- Hypocalcemia
- Hypokalemia
### Aminoglycoside Nephrotoxicity

**The risk factors for the aminoglycoside nephrotoxicity.**

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Treatment-related</th>
<th>Concomitant drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Longer treatment</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Reduced renal function</td>
<td>Higher dosages</td>
<td>Higher dosage diuretics</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Split dosages</td>
<td>Amphotericin</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Type of aminoglycoside</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Renal mass reduction</td>
<td>Elevated plasma drug concentrations</td>
<td>Cyclosporin</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td>Iodide contrast media</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td></td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td></td>
<td>Cephalosporin</td>
</tr>
</tbody>
</table>
Aminoglycoside Nephrotoxicity

3.8.1: We suggest not using aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available. (2A)

3.8.3: We recommend monitoring aminoglycoside drug levels when treatment with multiple daily dosing is used for more than 24 hours. (1A)
ACE Induced Renal Toxicity

- Hyperkalemia
- Hemodynamic-related renal failure

Etiologic factors
- Bilateral renal artery stenosis
- ↓ blood volume
- Chronic renal disease
- Concomitant NSAID therapy
- Old age
## Drugs Responsible for Acute Interstitial Nephritis

<table>
<thead>
<tr>
<th>ANTIMICROBIAL AGENTS</th>
<th>ANALGESICS</th>
<th>OTHERS</th>
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</thead>
<tbody>
<tr>
<td>PENICILINS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Aminopyrine</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Antipyrene</td>
<td></td>
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<tr>
<td>Aztreonam</td>
<td>Antrafenin</td>
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<tr>
<td>Carbenicillin</td>
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<td></td>
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<tr>
<td>Cloxacillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mezlocillin</td>
<td></td>
<td></td>
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<tr>
<td>Nafcillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxacillin*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericillin G*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(benzylpenicillin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs INCLUDING SALICYLATES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALICYLATES AND DERIVATIVES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (acetyl salicylic acid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANTICONVULSANTS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Common culprits

**ANTIBIOTICS**
- [Methicillin]
- Benzylpenicillin
- Ampicillin
- Ciproflaxacin
- Rifampicin
- Sulphonamides
- Co-trimoxazole

**NSAIDs**
- [Cimetidine]
- Omeprazole

**Frusemide**

**Phenindione**

---

*Comprehensive textbook of Nephrology, 2010*
TIN

WBCS casts

Diagnostic value of eosinophiluria
4 large series – 210 patients

<table>
<thead>
<tr>
<th></th>
<th>AIN</th>
<th>Not AIN</th>
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<tbody>
<tr>
<td>Eosinophiluria</td>
<td>29</td>
<td>19</td>
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<tr>
<td>No eosinophiluria</td>
<td>14</td>
<td>148</td>
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</tbody>
</table>
### Urinary Sediment Findings in AIN

(AIN 23/839 biopsies)

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age (y)/Sex</th>
<th>Cause</th>
<th>SCR (mg/dL)</th>
<th>UP (g/24 h)</th>
<th>WBC</th>
<th>RBC</th>
<th>RTEC</th>
<th>Casts</th>
<th>Cast Type</th>
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<tbody>
<tr>
<td>1</td>
<td>26/F</td>
<td>NSAID</td>
<td>0.7, 14.6</td>
<td>0.49</td>
<td>3-4</td>
<td>2-3</td>
<td>—</td>
<td>&gt;1/LPF</td>
<td>H, HG, G</td>
</tr>
<tr>
<td>2</td>
<td>60/F</td>
<td>NSAID</td>
<td>NA, 7.5</td>
<td>12.1</td>
<td>15-20</td>
<td>15-20</td>
<td>—</td>
<td>—</td>
<td>H, HG, G</td>
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<tr>
<td>3</td>
<td>75/M</td>
<td>Doxazosin</td>
<td>NA, 4.7</td>
<td>1.3</td>
<td>2-4</td>
<td>0-2</td>
<td>—</td>
<td>—</td>
<td>1/5-6 LPFs H, HG, G</td>
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<tr>
<td>4</td>
<td>31/M</td>
<td>Salazopyrin</td>
<td>1.5, 3.4</td>
<td>0.7</td>
<td>15-25</td>
<td>1-2</td>
<td>—</td>
<td>&gt;1/LPF</td>
<td>G, WBC</td>
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<tr>
<td>5</td>
<td>36/M</td>
<td>NSAID</td>
<td>NA, 2.3</td>
<td>0.44</td>
<td>4-5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>6</td>
<td>70/M</td>
<td>Ciprofloxacin</td>
<td>NA, 10</td>
<td>1.32</td>
<td>3-5</td>
<td>60-70</td>
<td>—</td>
<td>1/9-10 LPFs</td>
<td>H, RBC</td>
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<tr>
<td>7</td>
<td>51/F</td>
<td>NSAID</td>
<td>RN, 4.3</td>
<td>1.4</td>
<td>0-2</td>
<td>1-3</td>
<td>—</td>
<td>&gt;1/LPF</td>
<td>H, HG</td>
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<tr>
<td>8</td>
<td>69/F</td>
<td>NSAID</td>
<td>0.9, 4.3</td>
<td>2.3</td>
<td>3-5</td>
<td>&gt;100</td>
<td>—</td>
<td>—</td>
<td>1/7-10 LPFs H, HG, G</td>
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<tr>
<td>9</td>
<td>51/M</td>
<td>Unidentified</td>
<td>1.5, 2.8</td>
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<td>1/2-3 HPFs</td>
<td>H, HG, G, RTEC</td>
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<tr>
<td>10</td>
<td>72/F</td>
<td>NSAID</td>
<td>RN, 1.7</td>
<td>0.32</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1/LPF</td>
<td>H, HG</td>
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<tr>
<td>11</td>
<td>65/F</td>
<td>Unidentified</td>
<td>NA, 2.3</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&gt;1/LPF</td>
<td>H, HG</td>
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<tr>
<td>12</td>
<td>37/F</td>
<td>Unspecified antibiotic</td>
<td>1.1, 1.4</td>
<td>0.38</td>
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<td>1/7-3 LPFs</td>
<td>H, HG</td>
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<td>RN, 6.9</td>
<td>0.75</td>
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<td>15-20</td>
<td>1/8-10 HPFs</td>
<td>&gt;1/LPF</td>
<td>H, HG, G, RBC, RTEC</td>
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<tr>
<td>14</td>
<td>37/M</td>
<td>Salazopyrin</td>
<td>2.7, 3.4</td>
<td>0.41</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1/LPF</td>
<td>H, HG, fatty, RBC, RTEC</td>
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<td>15</td>
<td>70/M</td>
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<td>1.3, 3.0</td>
<td>0.84</td>
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<td>—</td>
<td>—</td>
<td>&gt;1/LPF</td>
<td>H, HG, G, RBC</td>
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<tr>
<td>16</td>
<td>74/M</td>
<td>Levofloxacin</td>
<td>NA, 2.4</td>
<td>0.32</td>
<td>6-12</td>
<td>2-3</td>
<td>—</td>
<td>&gt;1/LPF</td>
<td>H</td>
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<td>17</td>
<td>62/M</td>
<td>Amoxicillin</td>
<td>1.5, 7.0</td>
<td>0.32</td>
<td>—</td>
<td>35-45</td>
<td>—</td>
<td>1/9-10 LPFs</td>
<td>H, HG, G, RBC</td>
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<tr>
<td>18</td>
<td>69/M</td>
<td>Levofloxacin</td>
<td>0.9, 3.5</td>
<td>0.29</td>
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<td>1/2-3 LPFs</td>
<td>H, HG, G</td>
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<td>19</td>
<td>17/F</td>
<td>NSAID</td>
<td>RN, 1.9</td>
<td>0.88</td>
<td>2-4</td>
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<td>20</td>
<td>79/F</td>
<td>Proton pump inhibitor</td>
<td>NA, 8.5</td>
<td>0.8</td>
<td>8-12</td>
<td>—</td>
<td>1/9-10 HPFs</td>
<td>1/2-3 LPFs</td>
<td>H, HG, G, WBC, RTEC</td>
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<tr>
<td>21</td>
<td>32/M</td>
<td>Salazopyrin</td>
<td>NA, 1.0</td>
<td>0</td>
<td>5-10</td>
<td>—</td>
<td>—</td>
<td>1/2-3 LPFs</td>
<td>H, HG, WBC, RBC</td>
</tr>
</tbody>
</table>

Acute Interstitial Nephritis: Drug induced

Clinical Manifestation of Drug-Induced Acute Interstitial Nephritis

- Eosinophilia
- Extrarenal symptoms
- Mild proteinuria
- Pyuria
- Hematuria
- Macroscopic hematuria
- Oliguria
- Renal failure

Percentage of patients

Other drugs
Enhanced vasoconstriction: due to prostaglandin synthesis inhibition
- Interstitial nephritis
- Sodium and water retention
- Hyperkalemia
- Papillary necrosis
- Hypertension
- Nephrotic syndrome
NSAID-associated TIN

1. Heavy proteinuria (> 3.0g/d)
2. Tubulointerstitial infiltration on biopsy specimen: glomeruli well preserved
3. Nonoliguric course
4. Eosinophilia/eosinophiluria not common
5. Variable time (weeks to months) to development
6. Role of steroids in resolution is unclear
Chronic TIN: Pathology
Use of Clinical Decision Support Systems for Kidney-Related Drug Prescribing: A Systematic Review

Davy Tawadrous, BHSc,1,2 Salimah Z. Shariff, BCompSc, PhD,2,4
R. Brian Haynes, MD, PhD,3 Arthur V. Iansavichus, MLIS,2 Arsh K. Jain, MD, MSc,2,4
and Amit X. Garg, MD, PhD2,3,4

Performance in clinical practice of the kidney safety biomarkers that are qualified for use in preclinical toxicological evaluation.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Non-clinical* Qualified</th>
<th>Clinical Available**</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2M</td>
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<td>✓</td>
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<td>✓</td>
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<tr>
<td>CysC</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>KIM-1</td>
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<td>✓</td>
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<tr>
<td>RPA-1</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>TFF3</td>
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<td>✓</td>
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<tr>
<td>uALB</td>
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<td>✓</td>
</tr>
<tr>
<td>uTP</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* Qualified only in rats.
** Published data support their use in clinical practice; final consensus on their precise diagnostic and prognostic utility still awaits.
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- Iatrogenic renal diseases
- **Drugs acting on the kidney**
- Special issues
- Conclusion
Ceiling Dose/Effect

Fractional Excretion of Sodium (%)

Log \([\text{Diuretic}_{TL}]\)

Ceiling Effect

Ceiling \([\text{Diuretic}_{TL}]\)
Ceiling Dose/Effect

Determinants of Ceiling Dose

- Increased Potency
- Decreased Tubular Transport (e.g., ARF/CRF)
- Increased Binding to Urinary Proteins (e.g., Nephrotic Syndrome)

Decrease
Increase
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## Gadolinium in USA

<table>
<thead>
<tr>
<th>Gd-based contrast agent</th>
<th>Trade name</th>
<th>Structure</th>
<th>Estimated no. of administrations as of 2009 (millions)</th>
<th>Number of US reports of NSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide</td>
<td>Omniscan</td>
<td>Linear nonionic</td>
<td>&gt; 25.0</td>
<td>482</td>
</tr>
<tr>
<td>Gadoversetamide</td>
<td>Optimark</td>
<td>Linear nonionic</td>
<td>&gt; 2.5</td>
<td>35</td>
</tr>
<tr>
<td>Gadopentetate</td>
<td>Magnevist</td>
<td>Linear ionic</td>
<td>&gt; 50.0</td>
<td>195</td>
</tr>
<tr>
<td>Gadobenate</td>
<td>Multihance</td>
<td>Linear ionic</td>
<td>&gt; 2.5</td>
<td>1</td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>ProHance</td>
<td>Cyclic</td>
<td>&gt; 7.5</td>
<td>0</td>
</tr>
</tbody>
</table>
Risk Factors for CIN

- Proinflammatory states
  - infection
  - connective tissue diseases
  - major surgery
- Hypercoagulable states
- Vascular injury
- Liver failure
  - hepatorenal syndrome
  - liver transplantation
- Metabolic abnormalities
  - hyperphosphatemia
  - hypercalcemia
  - metabolic acidosis
  - iron overload
- Therapeutic agents
  - high-dosage ESA
  - intravenous iron
Can Gadolinium Be Given Safely to A Patient On Dialysis?

I believe that the risk of NSF is minimal at best by utilizing the following guidelines:

1. Avoid gadodiamide, gadoversetamide, and gadopentetate
2. Do not exceed 0.1 mmol/kg dose
3. Hemodialyze the day of and two consecutive days following gadolinium exposure

and I believe, “yes,” with reasonable certainty gadolinium can be given safely to a patient on dialysis.

Roger A. Rodby, said

Seminars in Dialysis 2011; 24 (4): 370-371
Chapter 74

Herbal and Over-the-Counter Medicines and the Kidney

Mark S. Segal, Xueqing Yu
## Kidney Syndromes Induced by Herbal Medicines

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Glycyrrhiza species (Chinese herbal teas, gancao, boui-ougi-tou)</td>
</tr>
<tr>
<td></td>
<td>Ephedra species (ma huang)</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>Traditional African medicine: toxic plants (Securidaca longipedunculata, Euphoria matabelensis, Callilepsis laureola, Cape aloes, or adulteration by dichromate)</td>
</tr>
<tr>
<td></td>
<td>Chinese medicine: Taxus celebica</td>
</tr>
<tr>
<td></td>
<td>Morocco: Takaout roumia (paraphenylenediamine)</td>
</tr>
<tr>
<td>Acute interstitial nephritis</td>
<td>Peruvian medicine (Uno degatta)</td>
</tr>
<tr>
<td></td>
<td>Tung Shueh pills (adulterated by mefenamic acid)</td>
</tr>
<tr>
<td>Fanconi syndrome</td>
<td>Chinese herbs containing AAs (Akebia species, Boui, Mokutsu)</td>
</tr>
<tr>
<td></td>
<td>Chinese herbs adulterated by cadmium</td>
</tr>
<tr>
<td>Papillary necrosis</td>
<td>Chinese herbs adulterated by phenylbutazone</td>
</tr>
<tr>
<td>Chronic interstitial renal fibrosis</td>
<td>Chinese herbs or Kampo containing AAs (Aristolochia species, Akebia species, Mutong, Boui, Mokutsu)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Datura species, Rhododendron molle (atropine, scopolamine)</td>
</tr>
<tr>
<td>Kidney stones</td>
<td>Ma huang (ephedrine)</td>
</tr>
<tr>
<td></td>
<td>Cranberry juice (oxalate)</td>
</tr>
<tr>
<td>Urinary tract carcinoma</td>
<td>Chinese herbs containing AAs</td>
</tr>
</tbody>
</table>
## Statin and Kidney

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal (mg/d)</th>
<th>CKD/ESRD</th>
<th>Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10 to 80</td>
<td>Dosage adjustment in patients with renal insufficiency is not necessary</td>
<td>No comment</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20 to 80</td>
<td>Dosage adjustments for mild to moderate renal impairment are not necessary; caution should be exercised with severe impairment</td>
<td>No comment</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>10 to 80</td>
<td>In patients with CrCl &lt; 30 ml/min, dosage increases &gt; 20 mg should be carefully considered and if deemed necessary should be supplemented cautiously</td>
<td>In patients taking CsA, therapy should begin with 10 mg/d and should not exceed 20 mg/d</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10 to 40</td>
<td>No comment</td>
<td>In patients taking CsA, therapy should begin with 10 mg and titration to higher dosages should be done with caution</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5 to 40</td>
<td>For patients who have severe renal impairment (CrCl &lt; 30 ml/min per 1.73 m²) and are not on hemodialysis, dosing should be started at 5 mg/d and not exceed 10 mg/d</td>
<td>In patients taking CsA, dosage should be limited to 5 mg/d</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5 to 80</td>
<td>Dosage adjustment should not be necessary in mild to moderate renal insufficiency; in patients with severe renal insufficiency, 5 mg/d should be the starting dosage with close monitoring if there is any titration</td>
<td>In patients taking CsA, therapy should begin with 5 mg/d and not exceed 10 mg/d</td>
</tr>
</tbody>
</table>
Statin and Kidney
Cochrane and EMBASE databases

- 80 trials (n 51 099) (statin versus placebo or no treatment).

<table>
<thead>
<tr>
<th></th>
<th>CKD</th>
<th>HD</th>
<th>Kid Tx</th>
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</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Mortality</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CV events</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR (CI)
Ciprofloxacin Induced AKI

- Acute interstitial nephritis
- Rarely:
  - Crystal nephropathy
  - Thrombotic microangiopathy
  - Tubular necrosis and apoptosis