Mechanisms of Drug Induced Acute Kidney Injury

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Objectives

- Describe the incidence of drug-induced nephrotoxicity
- List the categories of drug-induced nephrotoxicity
- Review urinary biomarker data for detecting subclinical and clinical kidney injury from cisplatin
- Introduce an application of precision medicine to describe changes to urinary biomarkers of kidney injury in reference to polymorphisms in genes encoding for transporter proteins
- Utilize pharmacokinetic parameters for predicting drug-induced kidney injury
Incidence of Nephrotoxicity

- Drug-induced nephrotoxicity accounts for up to 20% of all acute kidney injury (AKI) cases.
- The incidence of subclinical and chronic disease due to drugs is uncertain.
- Approximately 15% of patients in an intensive care unit will develop drug-induced AKI.
- The etiologies of the DI-AKI in one study were:
  - Diuretics 33%
  - NSAIDs 12%
  - Aminoglycosides 7%
  - Glycopeptides 1.4%
  - Contrast Media 48%

The Kidney is Vulnerable to Nephrotoxicity

- Excretion route for many drugs and metabolites
- Highly vascular (receives 25% of cardiac output)
- Proximal tubule cells are involved in uptake and efflux of drugs (drug transport)
- Kidney is metabolically active (drug metabolism)
- Urinary concentrating function serves to increase intraluminal concentrations of potential nephrotoxins
Drug-induced Kidney Injury Categories and Examples

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudo-Renal</td>
<td>Steroids, Tetracycline, Cimetidine, Trimethoprim</td>
</tr>
<tr>
<td>Hemodynamic (Pre-Renal)</td>
<td>ACE inhibitors, NSAIDs, Cyclosporin A</td>
</tr>
<tr>
<td>Glomerular</td>
<td>Gold, D-penicillamine, NSAIDs, hydralazine, bisphosphonates</td>
</tr>
<tr>
<td>Tubular Epithelial (ATN)</td>
<td>Aminoglycosides, Radiocontrast Media, Cyclosporin A, Anti-virals, <strong>Cisplatin</strong></td>
</tr>
<tr>
<td>Interstitial Nephritis</td>
<td>Diuretics, Antibiotics, NSAIDs, PP-inhibitors</td>
</tr>
<tr>
<td>Obstructive (Post-Renal)</td>
<td>Amphotericin B, Methotrexate, Anti-virals</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme
4. Acute tubular necrosis (ATN)

- Cellular degeneration and sloughing from proximal and distal tubules and dilatation of tubules
- Common form of drug-induced nephrotoxicity
- Kidney failure usually reversible
- UA: RBC, mild proteinuria, granular casts

Examples

- Aminoglycosides (antibiotic)
- Radiographic contrast media
- Amphotericin B (antifungal)
- **Cisplatin** (chemotherapeutic drug)
- Intravenous Immunoglobulins (IgG)
- Herbals
- NSAIDs
Cisplatin

- Cisplatin is a drug used to treat cancers by forming intra-strand crosslinks with DNA.

- Multiple pathologic mechanisms for nephrotoxicity are proposed:
  - tubular epithelial cell toxicity
  - vasoconstriction
  - inflammation

- Drug transporters on proximal tubules play a role in exposure of kidney to cisplatin.
  - Uptake transporters – entry into proximal tubule cells from blood: Organic Cation Transporter-2 (OCT2), Copper Transporter 1 (CTR1)
  - Efflux transporters – exit from proximal tubule cells to urine (MRP2 and MATE1).
Kidney Transporters as a Mechanism for Cisplatin Kidney Injury
Hypothesis 1: Novel urinary biomarkers as compared to serum creatinine/eGFR (clinical standard), can detect subclinical and clinical kidney injury post cisplatin administration.

- Evaluate a panel of novel urinary protein biomarkers to determine patterns of change up to 10 days after receiving cisplatin.
- Evaluate platinum in urine as a ”quasi” assessment of kidney exposures and non-protein biomarker.

Hypothesis 2: Genetic variants in key metabolic and transport pathways are biomarkers predict the risk of nephrotoxicity as assessed by clinical and novel protein and non-protein biomarkers in cisplatin-treated patients.

- Genotype patients prescribed cisplatin for a panel of relevant polymorphisms in cisplatin-specific metabolism and transport pathway genes.
- Evaluate cisplatin pharmacokinetics and kidney exposure (via urinary platinum excretion).
Patient Demographics for Biomarker Assessments (n=57)

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of patients</th>
</tr>
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<tbody>
<tr>
<td>Age, (mean ± SD)</td>
<td>56.6 ± 13.2 y</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
</tr>
<tr>
<td>Female</td>
<td>28</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>27.0 ± 6.0 kg/m²</td>
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<tr>
<td>Cisplatin dose (mean ± SD)</td>
<td>63.4 ± 22.8 mg/m²</td>
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<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>51</td>
</tr>
<tr>
<td>Hispanic</td>
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<tr>
<td>African American</td>
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<tr>
<td>Not reported</td>
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BMI, body mass index.

Urinary Excretion of Novel Nephrotoxicity Biomarkers Following Cisplatin Infusion. Urine was collected from n=57 patients prescribed cisplatin for various solid tumors. Urinary proteins were quantified by multiplex ELISA on a Magpix. Raw data are shown along with mean ± SD. * p <0.05 compared to 0 days.

## Changes to Urinary Biomarkers at Subsequent Cisplatin Cycles

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Group</th>
<th>Days</th>
<th>Baseline vs. Time points (Days)</th>
<th>Estimated Regression Coefficients</th>
<th>SE</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>KIM-1</strong></td>
<td>Initial</td>
<td>0</td>
<td>Intercept</td>
<td>1.14</td>
<td>0.47</td>
<td>0.0232</td>
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<tr>
<td></td>
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<td>3</td>
<td>3 vs. baseline</td>
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<td></td>
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<td>10</td>
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<tr>
<td></td>
<td>Subsequent</td>
<td>0</td>
<td>36 vs. baseline</td>
<td>1.21</td>
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<td>0.0261</td>
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<tr>
<td></td>
<td></td>
<td>3</td>
<td>39 vs. baseline</td>
<td>1.72</td>
<td>0.54</td>
<td>0.0017</td>
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<tr>
<td></td>
<td></td>
<td>10</td>
<td>46 vs. baseline</td>
<td>1.05</td>
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<tr>
<td><strong>Calbindin</strong></td>
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<td>Intercept</td>
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<td>5.77</td>
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<td></td>
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<td>3</td>
<td>3 vs. baseline</td>
<td>-1.38</td>
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<td><strong>TFF3</strong></td>
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<td></td>
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<td>10</td>
<td>46 vs. baseline</td>
<td>27</td>
<td>9.79</td>
<td>0.0067</td>
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</tbody>
</table>
Relationship between Changes in eGFR and Genotypes (n=206) in Patients receiving Cisplatin

**SLC22A2 – OCT2**

**SLC31A1 – CTR1**

Both are uptake transporters on basolateral membrane

Relationship between KIM-1 and \textit{SLC22A2/OCT2 (rs316019)} Genotype

Correlation between Peak Plasma Platinum and Urinary Platinum and Urinary Biomarkers of Kidney Injury

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Correlations between total peak [2 h] plasma and urinary platinum concentrations and urinary biomarker concentrations at days 3 and 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 3</strong></td>
<td></td>
</tr>
<tr>
<td>Urinary Pt</td>
<td>Plasma Pt</td>
</tr>
<tr>
<td>$R^2$</td>
<td>$r$</td>
</tr>
<tr>
<td>TFF-3</td>
<td>0.081</td>
</tr>
<tr>
<td>Albumin</td>
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<tr>
<td>NGAL</td>
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<tr>
<td>Osteopontin</td>
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<tr>
<td>Calbindin</td>
<td>0.16</td>
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<tr>
<td>Cystatin C</td>
<td>0.09</td>
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<tr>
<td>IL-18</td>
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<tr>
<td>KIM-1</td>
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<tr>
<td>Clusterin</td>
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<tr>
<td>β2M</td>
<td>0.49</td>
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<tr>
<td>GST-pi</td>
<td>0.001</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

$\beta 2M$, beta 2-microglobulin; GST-pi, glutathione S-transferase-pi; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; NGAL, neutrophil gelatinase-associated lipocalin; TFF3, trefoil factor 3

Ibrahim ME, et al. EJCP 2018;online Sept 15.
Analysis of Patient Level Data

Fig. 3. Use of Ondansetron (Ondan) in Patients Prescribed Cisplatin is Associated with Greater Loss of eGFR. Patients receiving varying antiemetic regimens (±Ondan) were evaluated for changes in eGFR at least 7 days following cisplatin. Statistical differences (mean±SD) were assessed by ANOVA.

Fig. 4. Enhanced Subclinical Kidney Injury in Patients Receiving Granisetron to Prevent Cisplatin-Induced Emesis. Oncology patients receiving palonosetron (n=16) or granisetron (n=16) were evaluated for changes in urinary biomarkers KIM-1 (A) and calbindin (B) following cisplatin infusion. Too few patients in this dataset received ondansetron or dolasetron to be included. Statistical differences (* p≤0.05) in data (mean±SD) were assessed by 2-way ANOVA.
**In Vitro Transport**

**Ondansetron Reduces Transepithelial Transport**

Fig. 8. Ondansetron Decreases ASP⁺ Transport in OCT2/MATE1-Expressing Cells. MDCK cells expressing human OCT2 and MATE1 were treated with ASP⁺ (25 μM) in the presence of ondansetron (0, 0.5, 2.5, 10 μM) on the basal side of the Transwell. Cimetidine (CIM, 50 μM) was used as a positive control inhibitor. Transport of ASP⁺ to the apical receiver side was monitored over 120 min. Data are shown mean ASP⁺ relative fluorescence units (RFU) ± SD.

**Ondansetron is a Potent Inhibitor of MATE1**

Fig. 5. Inhibition of ASP⁺ Uptake in Kidney Cells Expressing Empty Vector (EV), OCT2 or MATE1. Cells were exposed to increasing concentrations of ondansetron followed by ASP⁺ (10 μM) for 1 min. Data are shown as mean±SD. *p<0.05 compared to 0 μM.

**5-HT³As Do Not Inhibit MRP2 Activity**

Fig. 6. MRP2 Efflux is Unchanged in the Presence of 5-HT³As. HEK cells expressing empty vector or human MRP2 were treated with 10 or 50 μM of the 5-HT³As (only 50 μM data shown). Calcein AM efflux was quantified. MK-571 (100 μM) was used as a positive control inhibitor. Data are shown as mean±SD. *p<0.05 compared to control MRP2 cells.
Working Transporter Hypothesis

Fig. 1. Proposed mechanism for increased cisplatin toxicity by 5-HT₃ antagonists (5-HT₃A) due to preferential inhibition of MATE1 and reduced secretion of the highly electrophilic parent and aquated cisplatin species. Inhibition of OCT2, CTR1, and MRP2 transporters by 5-HT₃As is unlikely at clinically-relevant concentrations.
Clinical Study Scheme

- **Assessment of eligibility**
  - Consent solid tumor patients prescribed cisplatin regimens (n=72)

- **Randomization**

- **grani setron 2 mg po/IV; n=24**
- **ondansetron 8 mg po/IV; n=24**
- **palonosetron 0.25 mg IV; n=24**

- **Analyze**
  1. Biomarkers
  2. PK (cisplatin and 5HT3A)
  3. Genetics

- **Blood and Urine Samples**
  - (for Biomarkers, PK, Genetics)

- **Blood (5 mL)**
  - Will be collected for DNA extraction. Targeted genotyping for drug transporters (SLC22A12, ABCC2, SLC47A1) and metabolizing enzymes (GGT1, GSTP1) will be performed.

- **Blood (7.5 mL)**
  - Will be collected by IV at 0, 0.5, 1, 2, 4, 48, 72 h and 10 d (60 mL total) post cisplatin dosing for determination of total, bound and free cisplatin, 5HT3A, and clinical measures of AKI.

- **Urine**
  - Will be collected into specimen containers for up to 72 h after cisplatin to determine Pt and 5-HT3A recovery.
Summary and Conclusions

- Acute kidney injury is a recognized problem of exposure to nephrotoxic drugs.
- There are currently limited data, however, on the rates of subclinical injury and long-term outcomes on the kidney.
- Precision “genetic” medicine approaches targeted to drug specific transporter pathways can be used to inform about urinary biomarker changes after drug exposures.
- Relationships between drug concentrations or pharmacokinetics and urinary biomarkers can be applied to nephrotoxic drug exposures.
- Drug-drug can enhance the risks of drug-induced interactions in polypharmacy kidney injury; especially through uptake and efflux transporters in the kidney.
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Questions?
Case 2

- A 50 yo woman developed a right-hand cellulitis 3 days after a car door was closed on her hand. She was admitted to the hospital where blood and wound cultures were found to be positive for *Staphylococcus aureus*.
- She received 2 full days of nafcillin 2 g IV q4h and was discharged on dicloxacillin 500 mg po QD.
- Ten days after discharge, she returns to the ED complaining of malaise, fever, rash and blood in the urine.
Case 2

- The following laboratory values were found: BUN 39 mg/dL, SCr 2.3 mg/dL, WBC 18,000 cell/mm³ with 20% eosinophils.

- The urinalysis was positive for WBC’s, RBC’s, eosinophiluria and FeNa 3%.
What type of kidney injury would you suspect?

How should the kidney injury be managed?

What preventive options, if any, could have been undertaken to lower the risk of developing acute kidney injury?
Questions?
Cases
Case 1

- A 53 yo Caucasian woman with hypertension, coronary artery disease, and peripheral vascular disease.
- Prescribed hydrochlorothiazide 25 mg po qd, atorvastatin 10 mg po qd, and aspirin 325 mg po qd.
- At last week’s clinic visit, she had 2 consecutive BP readings of 187/96 and 193/95 mmHg, respectively, measured 20 minutes apart.
Case 1

- The patient’s primary care physician added lisinopril 40 mg po qd.
- She returns to the clinic today for her 1-week follow-up visit with complaints of dizziness, very little urine production and swelling in her ankles.
- BP is 94/43 mm Hg.
- An electrolyte panel was obtained and was significant for a BUN of 62 mg/dL and Scr 6.1 mg/dL.
What drugs might be implicated in the kidney injury?

What patient-related factors might have predisposed to acute kidney injury?

How should this patient’s acute kidney injury be managed?

Should losartan replace the lisinopril?
Classification of ADRs

- **Type A**
  - Predictable
  - Dose-dependent
  - E.g. ATN with aminoglycosides

- **Type B**
  - Unpredictable
  - Dose-independent
  - Idiosyncratic
  - E.g. AIN with proton pump inhibitors
1. Pseudo-Renal Disease

- ↑ BUN:Scr with maintenance of GFR
- ↑ BUN - increased catabolism
  - Corticosteroids
  - Tetracyclines
- ↑ Scr - inhibition of tubular creatinine secretion in kidney tubules
  - Cimetidine
  - Trimethoprim
2. Hemodynamic (Pre-Renal)

Drugs reverse the normal scenario:

- NSAIDs wipe out PGE; so more vasoconstriction at afferent site; reduced filtration pressure
- ACEI wipe out ANG II; so more vasodilation at efferent site; reduced filtration pressure
3. Glomerular disease

- **Clinical presentation**
  - Proteinuria, edema, and ↓ serum albumin due to urinary losses

- **Examples**
  - Gold (parenteral > po)
  - D-penicillamine
  - NSAIDs
  - Hydralazine
  - Bisphosphonates
  - Lithium
  - Targeted cancer therapies (Bevacizumab, Gefitinib, Imatinib)

- **Management**
  - Discontinue drug - proteinuria typically resolves
  - Prednisone 0.5-1 mg/kg x 2-4 weeks
Targeted Cancer Treatments

Targeted Cancer Therapies

- **VEGF targeted** – Bevacizumab (antibody to VEGF)
  - proteinuria, interstitial nephritis, thrombotic microangiopathy

- **EGFR targeted** – Gefitinib (inhibitor of EGFR), no toxicity seen with erlotinib and cetuximab
  - nephrotic syndrome, proteinuria, interstitial infiltration of lymphocytes, interstitial damage from the inhibition of normal turnover of tubular epithelial cells

- **PDGFR targeted** – Imatinib (inhibitor of PDGFR)
  - acute tubular necrosis, thrombotic microangiopathy, Fanconi syndrome, tubular vacuolization of both proximal and distal tubules
Aminoglycosides
Aminoglycosides

- Incidence 5-25%
- Clinical presentation
  - Gradual \(\uparrow\) SCr after 5-10 days of therapy
  - \(\downarrow\) serum magnesium and potassium (wasting)
- Pathogenesis
  - Proximal tubular epithelial damage \(\rightarrow\)
    obstruction of tubular lumen \(\rightarrow\) back-leak of glomerular filtrate
- Aminoglycosides are eliminated as unchanged drug in urine
- Administered intravenously
Aminoglycosides

- **Risk factors**
  - **Dosing**
    - Prolonged therapy
    - Large total cumulative dose
    - Trough concentrations > 2 mg/L (PK monitoring is useful)
  - **Predisposing conditions**
    - Pre-existing chronic kidney disease
    - Dehydration
    - Liver disease
    - Increased age
  - **Concomitantly prescribed nephrotoxic agents**
    - Amphotericin B, diuretics, vancomycin
Aminoglycosides

- Prevention
  - Once daily dosing
  - Alternate antibiotic
  - Avoid volume depletion
  - Limit total dose
  - Avoid concomitant nephrotoxic agents
Aminoglycosides

- Management
- Monitor SCr every 2-4 days
- Monitor drug concentrations
- Maintain fluid and electrolyte balance
- Severe cases - hemodialysis
Radiographic Contrast Media

- Incidence based on baseline SCr:
  - Normal SCr: < 1%
  - SCr > 1.5 mg/dL: 30-40%
  - SCr > 5 mg/dL: 70%

- Clinical presentation
  - Osmotic diuresis → tubular proteinuria, ↓ FeNa, ↑ SCr day 2-5, oliguria (50%)

- Pathogenesis
  - Direct tubular toxicity and vasoconstriction/renal ischemia

- Risk factors
  - Chronic kidney diseases e.g. diabetic nephropathy, CHF, dehydration, multiple myeloma, ↑ dose, hyperosmolar contrast agents
Iodinated Contrast Media

- **Lower osmolality** (iodixanol) or **nonionic** contrast agents have improved safety.

Antivirals

- **Nucleotide analogues:**
  - adefovir (hepatitis B), cidofovir (CMV retinitis), tenofovir (HIV)
- **Accumulate in tubular cells as organic anions**

![Chemical structures]

Adefovir  
Cidofovir  
Tenofovir
Anti-viral Drugs: Kidney Toxicity Mediated by Transporters

5. Interstitial Nephritis (AIN)

- Mononuclear cell infiltrate with edema in the renal interstitium.
- Over two-thirds of AIN is drug-induced.
- Prolonged injury can cause permanent injury.
- Incidence: 3-14% of AKI

Clinical presentation

- Onset: 17 (2-44) days after initiating drug
- Signs and symptoms
  - Fever (75%), maculopapular rash (25%), eosinophilia (80%), pyuria/hematuria (90%), low-level proteinuria (90%), eosinophiluria (often absent), arthralgias
Interstitial Nephritis

Examples
- **Antibiotics:** Penicillins, sulfonamides, cephalosporins, fluoroquinolones, rifampicin.
- **Diuretics:** Thiazides, furosemide.
- **Miscellaneous:** Proton pump inhibitors, protease inhibitors, NSAIDs, phenytoin, cimetidine, mefenamic acid, allopurinol, lithium.
- **Cancer Drugs:** TKIs, immune checkpoint inhibitors, proteasome inhibitors.

Pathogenesis
- Allergic hypersensitivity

Risk factors
- None – idiosyncratic

Findings
- Urine: WBC and RBC casts in urine
- $\uparrow$ Fractional excretion of Na+ (FeNa >1%)
- Mild-high proteinuria

Prevention
- Careful monitoring

Management
- D/C, prednisone 0.5-1 mg/kg for 1-4 weeks
6. Obstruction (Post-renal)

- Mechanical obstruction to urine flow
  - Crystals precipitate within tubules, ureters or bladder

- Clinical presentation
  - Pain, hematuria

- Cancer Chemotherapy
  - Due to tissue degradation products
  - Rapid onset of oliguria/anuria
  - Prevention: hydration, urine pH>7, allopurinol
Crystal-Producing Drugs

- Indinavir
- Acyclovir
- Sulfonamides
- Methotrexate
- Triamterene
- Ciprofloxacin
Obstructive (Post-renal)

- **Acyclovir - antiviral**
  - IV and high dose po
  - Needle-shaped crystals

- **Indinavir – HIV protease inhibitor**
  - Incidence of AKI is 10%
  - Rectangular crystals
  - Prevention: high urine volume (2-3 L fluid), soluble at acid pH but urine acidification not practical
  - Reduce dose if on CYP3A drugs
Indinavir Crystals
Other Representative Crystals

Sulfonamides

Ciprofloxacin
Clinical Study (R21 DK093903)

- Prospective study with patients scheduled to begin outpatient chemotherapy for solid tumors with IV cisplatin ≥30 mg/m² every 3-4 weeks.
- eGFR (MDRD) calculated at baseline > 60 mL/min/1.73 m².
- Standard hydration pre- and post-treatment with saline (1-2 L) across patients.
- Inclusion criteria: 1) Age ≥18 years, 2) hemoglobin ≥10 g/dL, 3) no consumption of grapefruit juice or alcohol within 7 days, 4) no history of alcohol consumption of >14 drinks/week, 5) no history of organ transplantation or kidney dialysis, 6) willingness to comply with study, 7) not pregnant or lactating, 8) no changes in medications within previous 4 weeks, and 9) normal liver function (ALT and AST <2x ULN).
- Exclusion criteria: 1) diagnosis of kidney cancer, 2) previous exposure to platinum-based chemotherapy, 3) herbal supplement use, 4) exposure to other known nephrotoxins (including contrast agents) within the previous 30 days, and 5) concurrent use of inhibitors of transport proteins.