Drug Induced Kidney Injury

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UC San Diego
Outline

1. Phenotype standardization for drug induced kidney disease
2. Discuss the epidemiology and mechanism of some common drug induced kidney injuries
3. Review the importance of causality assessment of adverse effects
A 53-year-old woman transferred from a community hospital for sepsis secondary to a recurrent LLE cellulitis. PMH includes ORIF L ankle, recurrent LLE cellulitis, HTN and hypothyroidism. At the community hospital she was treated with IV clindamycin. She has worsening pain, erythema, swelling to LLE with new open wound to left lateral ankle. Home medications include carvedilol 12.5 mg po bid, lisinopril 20 mg po daily, clindamycin 300 mg po three times daily, levothyroxine 137 mcg po daily. Her vital signs include BP 90/65 mmHg, heart rate 98 bpm, RR 16, O2 sat 98%, pain score 8/10. She is started on IV fluids, vancomycin (goal trough 15-20 mg/L) and piperacillin/tazobactam. Her oral anti-hypertensives are discontinued. On day 2 of her admission she develops AKI, which continues to worsen over the next few days.
Clear as Mississippi Mud?

<table>
<thead>
<tr>
<th>Labs</th>
<th>Adm</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
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</thead>
<tbody>
<tr>
<td>Scr</td>
<td>0.89</td>
<td>1.68</td>
<td>2.29</td>
<td>2.35</td>
<td>2.31</td>
<td>2.34</td>
<td>2.45</td>
</tr>
<tr>
<td>GFR</td>
<td>&gt;60</td>
<td>32</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>[Vanc]</td>
<td></td>
<td>18.8</td>
<td></td>
<td>20.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>22.4</td>
<td>21.9</td>
<td>13.1</td>
<td>12.8</td>
<td>14.7</td>
<td>12.6</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Is this vancomycin nephrotoxicity?
Drug Induced Kidney Injury Occurs Frequently

- Large AKI observational studies have demonstrated 14-28% of patients develop drug induced kidney injury
- AKI-EPI was an international study of 1802 critically ill patients
  - 57.3% of ICU patients developed AKI
  - Nephrotoxic drugs were the etiology in 14.4%
  - 1/3 of patients were treated with diuretics, 11.9% NSAIDs, AMG 6.8%, glycopeptides 1.4%, and contrast media 2.1%
  - 47.7% patients had residual injury at discharge

Awdishu L. Curr Opin Crit Care. 2017
Hoste E et al. Intensive Care Med. 2015
Uchino S et al. JAMA 2005
Mehta RL et al. Kidney Int 2004
Waikar S et al. CJASN. 2008
Re-defining Drug Induced Kidney Disease Phenotypes

- Phenotype standardization based on the clinical presentation of the injury and biomarker change
Drug Injury Can Be Acute, Subacute or Chronic

Acute: 1-7 days
Subacute: 8-90 days
Chronic: > 90 days
AKI Phenotype
Primary Defining Criteria

Rise in Scr that presents as or progresses to AKIN Stage 2 (KDIGO) or higher in relation to drug exposure
- 2-2.9 x reference Scr
- If child has baseline Scr < 0.5 mg/dL, must double Scr to get to at least 0.5 mg/dL or above

Decline in Scr as defined by Stage 2 (KDIGO)
- Decline by 50% from peak creatinine over 7 days
- For pediatrics peak creatinine must be at least 0.5 mg/dL
- Must have decline in relationship to change in drug dosing (reduction, or stopping drug)

Kidney Biopsy findings consistent with
- nephrotoxic,
- allergic or
- mixed pattern

OR

# Drug Induced Kidney Disease

## AKI
- ATN
- Aminoglycosides
- Amphotericin
- Cidofovir
- Cisplatin
- CNI
- Methotrexate
- Vancomycin

## Glomerular
- Lupus-like syndrome
- Hydralazine
- Membranous
- NSAIDs
- TMA
- CNI
- Pamidronate
- Gencitabine

## Tubular
- Fanconi like
- Cisplatin
- Ifosfamide
- Tenofovir
- DI
- Lithium

## Nephrolithiasis
- Crystalluria/Obstructive
- Indinavir
- Atazanavir
- Acyclovir
- SMX/TMP
Vancomycin Nephrotoxicity

- Glycopeptide antibiotic isolated from *Streptomyces orientalis*
- “Mississippi Mud”
  - Improvement in purity from 70 to 95%
- **Recognition:** 5-43% depending on definition employed
- **Risk:** Dose > 4 g/day Trough > 15 mg/L, CKD, duration of therapy, concomitant nephrotoxins
- **Response:** Minimize concurrent nephrotoxins, dose < 4 g/day and trough closer to 15 mg/L, switch abx
- **Renal Support:** 0-7.1% require dialysis
- **Rehabilitation:** resolution 21-72.5%

Gomes et al. Pharmacotherapy. 2014
Meaney et al. Pharmacotherapy. 2014
Larger Vancomycin Doses (at Least Four Grams per Day) Are Associated with an Increased Incidence of Nephrotoxicity

Thomas P. Lodise,1,2* Ben Lomaestro,3 Jeffrey Graves,1 and G. L. Drusano2

Dose > 4 g/day OR 4.4[1.7-11.8], p=0.003 for occurrence of nephrotoxicity

**Relationship between Vancomycin Trough Concentrations and Nephrotoxicity: a Prospective Multicenter Trial**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio for nephrotoxicity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough concn, &gt;15 mg/liter</td>
<td>3.643</td>
<td>1.749–7.587</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1.055</td>
<td>0.444–2.503</td>
</tr>
<tr>
<td>LOT with vancomycin</td>
<td>1.002</td>
<td>1.000–1.004</td>
</tr>
<tr>
<td>Other nephrotoxins given</td>
<td>1.201</td>
<td>0.606–2.381</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.986</td>
<td>0.488–1.995</td>
</tr>
<tr>
<td>Race (black)</td>
<td>2.589</td>
<td>1.278–5.244</td>
</tr>
<tr>
<td>ICU stay</td>
<td>1.408</td>
<td>0.700–2.834</td>
</tr>
<tr>
<td>Age</td>
<td>0.999</td>
<td>0.978–1.020</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.253</td>
<td>0.051–1.243</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.284</td>
<td>0.027–2.965</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.326</td>
<td>0.402–13.456</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>1.283</td>
<td>0.217–7.574</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.666</td>
<td>1.017–13.208</td>
</tr>
<tr>
<td>Diabetes without end organ damage</td>
<td>1.038</td>
<td>0.512–2.104</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>1.079</td>
<td>0.106–10.946</td>
</tr>
<tr>
<td>Any tumor</td>
<td>1.153</td>
<td>0.313–4.249</td>
</tr>
<tr>
<td>Mild hepatic disease</td>
<td>3.856</td>
<td>0.179–83.135</td>
</tr>
<tr>
<td>Moderate hepatic disease</td>
<td>0.280</td>
<td>0.021–3.716</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>5.877</td>
<td>1.370–25.204</td>
</tr>
<tr>
<td>AIDS</td>
<td>0.697</td>
<td>0.032–15.063</td>
</tr>
</tbody>
</table>

**Multicenter, prospective observational trial of 206 patients**

**Incidence of nephrotoxicity:**
- 8.9% in low trough group
- 29.6% in high trough group

UC San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences
Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

Prospective, double blind controlled multicenter international trial

1. Laboratory evidence of AKI in 8.4% of linezolid treated patients versus 18.2% of vancomycin treated subjects.

2. In patients with eGFR < 50 mL/min, 13.8% in linezolid versus 16.2% in vancomycin

3. In patients with eGFR > 50 mL/min, 5.6% in linezolid versus 18.8% in vancomycin

Higher clinical success in patients with ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus* treated with linezolid compared with vancomycin: results from the IMPACT-HAP study

Mean(SD) vancomycin trough 13 mg/L on Day 3

Peyrani *et al.* Critical Care 2014, 18:R118
http://ccforum.com/content/18/3/R118
Effect of vancomycin serum trough levels on outcomes in patients with nosocomial pneumonia due to *Staphylococcus aureus*: a retrospective, post hoc, subgroup analysis of the Phase 3 ATTAIN studies

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin trough level (μg/mL), n/N (%)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 10</td>
<td>10 to &lt; 15</td>
</tr>
<tr>
<td>All patients</td>
<td>21/30 (70)</td>
<td>18/33 (55)</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>13/20 (65)</td>
<td>15/26 (58)</td>
</tr>
<tr>
<td>MRSA</td>
<td>14/26 (54)</td>
<td>11/20 (55)</td>
</tr>
<tr>
<td>MRSA based on median trough levels collected up to study Day 4</td>
<td>4/30 (13)</td>
<td>8/33 (24)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>0/30 (0)</td>
<td>1/33 (3)</td>
</tr>
<tr>
<td>Renal adverse events†</td>
<td>0/30 (0)</td>
<td>0/33 (0)</td>
</tr>
<tr>
<td>Significant increases in serum creatinine‡</td>
<td>0/30 (0)</td>
<td>0/33 (0)</td>
</tr>
<tr>
<td>Increase 2 to &lt; 3 times from baseline</td>
<td>0/30 (0)</td>
<td>0/33 (0)</td>
</tr>
<tr>
<td>Increase ≥ 3 times from baseline</td>
<td>3/30 (10)</td>
<td>5/33 (15)</td>
</tr>
</tbody>
</table>
| Deaths                   | 10 (6, 12)                                | 11 (8, 14) | 11 (8, 15) | 0.14,

Barriere et al. BMC Infectious Diseases 2014;14:183
Meta-analysis of Vancomycin Nephrotoxicity

Prior Knowledge of Vancomycin Nephrotoxicity Suggests Oxidative Stress

Induces oxidative stress

1. Vancomycin administered to rats resulted in ↑NAG, ↓SOD and catalase
   • Amelioration by administering hexamethylenediamine superoxide dismutase in rats
     • Scr 0.293 ± 0.03, 0.466 ± 0.056 and 0.317 ± 0.020, in controls, vanco, and vanco treated with AH-SOD, respectively
   • Amelioration by administering erdosteine in rats
   • Genomic analysis reveals decreases in gene transcription of SOD, CAT and glutathione peroxidase

2. Increases oxygen consumption and [ATP] in mitochondria

Is “trapped” in tubular cells

• Transported by OCT across basolateral membrane but no active transport identified across brush border membrane

4 King et al. Toxicology in Vitro. 2004; 18(6): 797-803
Histopathological Evidence of Vancomycin Nephrotoxicity

Christine Dieterich et al. Toxicol. Sci. 2008;107:258-269
Pharmacogenomics Point to Gap Junction in Vancomycin Nephrotoxicity

• SNP (rs2789047) on chromosome 6 in patients of Northern European ancestry associated with AKI stage 1 ($p=1.1\times10^{-7}$)

• Region of gene GJA1, which encodes for connexin43, a gap junction protein in renal tubules

• Gap junctions have been shown to contribute to tubular injury associated with aminoglycosides

• Exact role in enhancing injury has not been fully elucidated
  • Transport of toxicants to surrounding cells and transmitting damage signals

New Findings of Obstructive Casts with Vancomycin Nephrotoxicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
<td>F</td>
<td>G</td>
<td>H</td>
<td>I</td>
</tr>
<tr>
<td>Sex</td>
<td>W</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>W</td>
<td>M</td>
<td>M</td>
<td>W</td>
</tr>
<tr>
<td>Age, yr</td>
<td>48</td>
<td>45</td>
<td>19</td>
<td>69</td>
<td>46</td>
<td>73</td>
<td>69</td>
<td>66</td>
<td>46</td>
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<tr>
<td>Initial Clinical Context</td>
<td>Meningitis</td>
<td>Sepsis</td>
<td>Septic arthritis</td>
<td>Septic arthritis</td>
<td>Pneumonia</td>
<td>Sepsis</td>
<td>Fever and neutropenia</td>
<td>Septic arthritis</td>
<td>Fever and neutropenia</td>
</tr>
<tr>
<td>Circulatory Shock</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SC at Renal Biopsy, mg/dl</td>
<td>6.2</td>
<td>3.8</td>
<td>Dialysis</td>
<td>13</td>
<td>Dialysis</td>
<td>3.2</td>
<td>5.7</td>
<td>4.7</td>
<td>4.2</td>
</tr>
<tr>
<td>SV Levels, mg/L</td>
<td>42</td>
<td>35</td>
<td>106</td>
<td>18.9</td>
<td>57.6</td>
<td>51.5</td>
<td>50</td>
<td>51</td>
<td>87</td>
</tr>
<tr>
<td>Vancomycin Therapy</td>
<td>19 d</td>
<td>3 d</td>
<td>10 d</td>
<td>3 d</td>
<td>14 d</td>
<td>8 d</td>
<td>7 d</td>
<td>12 d</td>
<td>3 d</td>
</tr>
<tr>
<td>Duration (Dosage)</td>
<td>(4 g/d)</td>
<td>(NA)</td>
<td>(NA)</td>
<td>(2 g/d)</td>
<td>(1.5 g/d)</td>
<td>(2 g/d)</td>
<td>(NA)</td>
<td>(NA)</td>
<td>(3 g/d)</td>
</tr>
<tr>
<td>Vancomycin Withdrawal</td>
<td>7</td>
<td>7</td>
<td>20</td>
<td>10</td>
<td>27</td>
<td>17</td>
<td>15</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>to Renal Biopsy, d</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Nephrotoxic Drugs</td>
<td>No</td>
<td>No</td>
<td>G</td>
<td>G</td>
<td>G,C</td>
<td>G</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dialysis</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Outcome</td>
<td>RRF</td>
<td>Death</td>
<td>RRF</td>
<td>Death</td>
<td>Death</td>
<td>RRF</td>
<td>RRF</td>
<td>Death</td>
<td>RRF</td>
</tr>
</tbody>
</table>

Luque Y et al. JASN 2017
Vancomycin Causes Obstructive Cast Nephropathy

Proteinaceous casts in tubular lumen

Nano to microspherical formations corresponding to vancomycin spectral signature

Co-localized with uromodulin and found in Bowman’s space

CD68+ macrophage infiltrate surrounding casts and in interstitium

Luque Y et al. JASN 2017
Aminoglycoside Nephrotoxicity

- AMG undergo filtration with reabsorption and accumulation in the renal cortex.
- AMG induce apoptosis and necrosis of tubular epithelial cells, alter water and solute transport, reduce RBF and GFR
- Recognition: 12-25% depending on definition employed
- Risk: Age, DM, CKD, CHF, volume depletion, sepsis, liver disease, frequency, duration, trough > 2 mcg/mL, concomitant vancomycin, gent>tobra>amikacin
- Response: Minimize concurrent nephrotoxins, once daily dosing, short duration, switch abx, avoid midnight-7am administration
- Renal Support: No difference in dialysis requirements
- Rehabilitation: 4-28% mortality, unresolved AKI

Schentag JJ et al. Antimicrobial agents and chemotherapy. 1982
Oliveira JF et al. Antimicrobial agents and chemotherapy. 2009
Recovery is Incomplete After Aminoglycoside Associated Kidney Injury

Retrospective study of 562 adults who received AMG > 5 days

<table>
<thead>
<tr>
<th>Outcome</th>
<th>% or Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>12</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Duration of AKI</td>
<td>7 (4-12) days</td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>LOS</td>
<td>34 (19-66) days</td>
</tr>
<tr>
<td>Mortality</td>
<td>28</td>
</tr>
</tbody>
</table>

NSAID Associated Kidney Injury

• NSAID users may develop renal adverse effects including: AKI, AIN, nephrotic syndrome, renal papillary necrosis
• NSAIDs are divided into Cox-2 selective and non selective agents
• Risk factors: volume depletion, CHF, hypotension, specific nsaids (indomethacin, ibuprofen, rofecoxib), high doses, duration of use, multiple nsaid user
• Rehabilitation: typically reversible, some develop CKD
• Several population-based studies have examined the association of NSAIDs with AKI
## Summary of Select Population Studies for NSAID Associated Kidney Injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition of AKI</th>
<th>Incidence of AKI</th>
<th>Risk Estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huerta, 2005</td>
<td>Diagnostic codes for AKI</td>
<td>1.1/10,000 person-years</td>
<td>3.23 [1.79-5.82]</td>
</tr>
<tr>
<td>Schneider, 2006</td>
<td>Diagnostic codes for AKI</td>
<td>1.48/1,000 person-years</td>
<td>2.05 [1.61-2.60]</td>
</tr>
<tr>
<td>Winkelmayer, 2008</td>
<td>Diagnostic codes for AKI</td>
<td>0.52% in 45 days of follow-up</td>
<td>1.52-2.23 for different agents compared to celecoxib</td>
</tr>
<tr>
<td>Lafrance, 2009</td>
<td>Scr, AKIN</td>
<td>3.77/1,000 person-years</td>
<td>1.82 [1.68-1.98]</td>
</tr>
</tbody>
</table>
PPI Associated Kidney Injury

- Among the most widely prescribed medications in the U.S. with 95 million prescriptions in 2009
- Considered generally safe
- Often taken by patients for an inappropriately long period of time
- Acute interstitial nephritis has been reported in case reports and series
- Several population-based studies have examined the association of PPIs with AKI or CKD
### Summary of Select Population Studies for PPI Associated Kidney Injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Injury</th>
<th>Definition of AKI and/or CKD</th>
<th>Incidence of AKI and/or CKD</th>
<th>Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoniou, 2015</td>
<td>AKI</td>
<td>Diagnostic codes</td>
<td>13.49/1,000 person-years</td>
<td>2.52 [2.27-2.79]</td>
</tr>
<tr>
<td></td>
<td>AIN</td>
<td></td>
<td>0.32/1,000 person-years</td>
<td>3 [1.47-6.14]</td>
</tr>
<tr>
<td>Lazarus, 2016</td>
<td>CKD</td>
<td>Diagnostic codes</td>
<td>14.2/1,000 person-years</td>
<td>1.5 [1.14-1.9]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eGFR &lt; 60 mL/min/1.73m²</td>
<td>20.1/1,000 person-years</td>
<td>1.17 [1.12-1.23]</td>
</tr>
<tr>
<td></td>
<td>AKI</td>
<td>Diagnostic codes</td>
<td>10.9/1,000 person-years</td>
<td>1.64 [1.22-2.21]</td>
</tr>
<tr>
<td>Xie, 2016</td>
<td>CKD</td>
<td>eGFR &lt; 60 mL/min/1.73m²</td>
<td>36.83/1,000 person-years</td>
<td>1.28 [1.23-1.34]</td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
<td>Diagnostic codes</td>
<td>0.41/1,000 person-years</td>
<td>1.96 [1.21-3.18]</td>
</tr>
<tr>
<td></td>
<td>AKI</td>
<td>Scr 0.3 mg/dL or 50% in 30 days</td>
<td></td>
<td>2.15 [2.00-2.32]</td>
</tr>
<tr>
<td>Xie, 2017</td>
<td>CKD</td>
<td>eGFR &lt; 60 mL/min/1.73m²</td>
<td>26.6/1,000 person-years</td>
<td>1.29 [1.22-1.36]</td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
<td>Diagnostic codes or 50% decrease in GFR</td>
<td>4.83/1,000 person-years</td>
<td>1.35 [1.19-1.53]</td>
</tr>
<tr>
<td>Lee, 2016</td>
<td>AKI</td>
<td>Scr 0.3 mg/dL in 48 hours or 50% in 7 days</td>
<td>20% in PPI, 18% H2RA, 16% controls in critically ill patients</td>
<td>1.02 [0.91-1.13]</td>
</tr>
</tbody>
</table>
Cisplatin is Metabolized to a Reactive Thiol Resulting in Tubular Toxicity

OCT-2

Pabla N. Kl. 2008;73:994-1007
Cisplatin Nephrotoxicity is Frequent and Often Irreversible

- **Recognition:** 58% in pediatrics, 43.5% in adults, onset within 10 days
- **Risk:** Age, race (AA), CKD, concomitant nephrotoxins, prior platinum exposure
- **Response:** Minimize concurrent nephrotoxins, correct hypomagnesemia, hydration with NS, amifostine (donates a protective thiol)
- **Renal Support:** Most will not require dialysis
- **Rehabilitation:** Recovery in 30%, partial recovery 24%, may take 6 months to recover some have persistent drop in GFR

Hansen SW et al. J Clin Oncol. 1988;6(11);1728
Anti-VEGF Nephropathy

**Recognition:** Case reports with bevacizumab for various malignancies
- Developed within 3-17 months of drug exposure
- All developed proteinuria
  - > 1 gram/day in 5/6
  - > 2 grams/day in 4/6
  - Nephrotic in 2/6
- 50% developed HTN, 50% developed renal failure
- TMA was noted in all 6 patients

**Response:** Renal findings improved upon withdrawal of bevacizumab
- Validated in VEGF knockout mouse
  - Disruption of glomerular endothelial cells, loss of glycocalyx, slit diaphragm function

Eremina V et al. NEJM, 2008
Check-point Inhibitors Aid in Tumor Destruction through Proliferation of T-cells but cause Autoimmunity and ATIN

Inhibition of checkpoints in immune system leads to autoimmunity and reactivation of memory T-cells previously primed by exogenous drug exposure.
PD-1 Inhibition

- PD-1 antibodies
  - Nivolumab for advanced melanoma
  - Pembrolizumab for NSCLC
- PD-1 down-regulates effector T cell function by engaging ligands PD-L1 on immune cells and PD-L2 on dendritic and macrophages
- PD-1 signaling is essential to tolerance of self antigens
  - PD-1 knockout mice develop GN
- Incidence of grade 3/4 nephrotoxicity in clinical trials ranging from 0.4% to 3% without identifying a clear cause
- Case series of 6 patients with biopsy proven AIN after 3 months to 1 year of PD1 inhibition
  - 5 patients on PPIs
  - Treated with steroids and most resolved kidney function

Perazella et al. AJKD 2016; 68(2):287-291
Checkpoint Inhibitor Associated AKI

- Case series of 13 patients
  - Overall incidence of 2.2% for AKI
  - AKI onset 21-245 days
  - Pyuria in > 50%

Causality Assessment of Adverse Events

Most cases concern suspected adverse drug reactions.

Few adverse reactions are 'certain' or 'unlikely'

Drug Induced AKI

Patient susceptibilities

• Age
• Race/Ethnicity
• Genetic predisposition

Disease Susceptibilities

• Concurrent AKI Risk Factors
• Underlying Illness and competing bias

Multidrug injury Process of Care Complexities

• Incomplete data on exposures
• Reference creatinine
• Lack of diagnostics
• Biopsies
• Drug Concentrations
• Measures of immune reactivity
• Genetic profiling
• PK modeling
Adjudication is Critical to Understanding the True Incidence of Drug Induced Kidney Disease

- Using EHR and standardized criteria to detect nephrotoxicity using rules based algorithms
- Electronic detection ≠ causality
- Adjudication is required to move from association closer to causality
- 32% of vancomycin exposures detected as nephrotoxicity, adjudication case rate 8.4%

Austin Bradford-Hill Criteria for Causal Association

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experimental evidence
9. Analogy
VEGF and PARP Inhibitor

64F with metastatic ovarian ca referred for evaluation of proteinuria. She was diagnosed with papillary serous cancer of ovary in 2014, Cr ~ 0.6 at that time and no proteinuria, treated with carboplatin and paclitaxol in the past (2014-2016), Cr up to 0.7-0.8 in the last 2 years, started on Avastin and olaparib in 5/17, proteinuria has been progressively rising, most recent up to 1gm. Most likely proteinuria is due to Avastin and or olaparib, but it is still relatively low level and Cr is relatively stable. BP up since adding Avastin. Overall proteinuric CKD 2-3 likely due to Avastin and or olaparib.
Temporality is Key to Drug Induced Injury
# Naranjo Scale for Causality

To assess the adverse drug reaction, please answer the following questions and give pertinent subscores for each drug.

<table>
<thead>
<tr>
<th>Question</th>
<th>Question Points</th>
<th>Subscores</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Are there previous conclusive reports on this reaction?</td>
<td>Yes: +1, No: 0,</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>DoNot Know: 0</td>
<td>Drug 2:</td>
</tr>
<tr>
<td></td>
<td>Drug 3:</td>
<td></td>
</tr>
<tr>
<td>(2) Did the adverse event appear after the suspected drug was administered?</td>
<td>+2, -1, 0</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>Drug 2:</td>
<td>Drug 3:</td>
</tr>
<tr>
<td>(3) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1, 0, 0</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>Drug 2:</td>
<td>Drug 3:</td>
</tr>
<tr>
<td>(4) Did the adverse reaction reappear when the drug was re-administered?</td>
<td>+2, -1, 0</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>Drug 2:</td>
<td>Drug 3:</td>
</tr>
<tr>
<td>(5) Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1, +2, 0</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>Drug 2:</td>
<td>Drug 3:</td>
</tr>
<tr>
<td>(6) Did the reaction reappear when a placebo was given?</td>
<td>-1, +1, 0</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>Drug 2:</td>
<td>Drug 3:</td>
</tr>
<tr>
<td>(7) Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1, 0, 0</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>Drug 2:</td>
<td>Drug 3:</td>
</tr>
<tr>
<td>(8) Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?</td>
<td>+1, 0, 0</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>Drug 2:</td>
<td>Drug 3:</td>
</tr>
<tr>
<td>(9) Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1, 0, 0</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>Drug 2:</td>
<td>Drug 3:</td>
</tr>
<tr>
<td>(10) Was the adverse event confirmed by any objective evidence?</td>
<td>+1, 0, 0</td>
<td>Drug 1:</td>
</tr>
<tr>
<td></td>
<td>Drug 2:</td>
<td>Drug 3:</td>
</tr>
</tbody>
</table>

Add subscores from each column to calculate the Naranjo score for respective drug:
(Score 0: Unlikely, Score 1-4: Possible, Score 5-8: Probable, Score 9-10: Definite)
Conclusions

• Drug induced kidney injury occurs frequently, is multifactorial and may be associated with residual injury
• Recognition of risk factors is key to reduce risk and improve recovery
• Causality assessment is critical to identifying the culprit drugs and minimizing future exposures