Drug Induced Nephrotoxicity

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"First Do No Harm": Primum No Nocere

Hippocratic Oath?

I will use treatment to help the sick according to my ability and judgment, but never with a view to injury.

"The physician must ... have two special objects in view with regard to disease, namely, to do good or to do no harm."

about a boy whose severe epilepsy, unresponsive to medications that resulted in significant side effects, eventually controlled by a ketogenic diet

Thomas Syndenham
The English Hippocrates
Described Syndenham’s Chorea (St Vitus’s Dance)
How Can A Physician do Harm?

Every office visit ends ....with 1.6 prescriptions!
unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use
Adverse Drug Reactions

Direct Cause of 3 – 7% of Hospitalizations

Occurs in 10 – 20% of Hospitalizations
Adverse Drug Reactions

ADEs: Avoidable medical problem

2.2 MILLION severe adverse drug events per year

FOURTH leading cause of death in the U.S.

100,000 deaths per year by properly prescribed drugs

80,000 deaths per year by improperly prescribed drugs

330 million dollars/year
"WE HAVE MET THE ENEMY AND HE IS US."

— POGO
Adverse Drug Reactions

Type A
- 80% of all ADRs
- Dose Dependent
- Predictable based on comorbid conditions, genetics and synergistic medications

Type B
- 20% of all ADRs
- Idiosyncratic
- Unpredictable
The Kidney is at Increased of Nephrotoxicity Compared to other Organs
Prevalence of Drug Induced Nephrotoxicity as a Cause of Acute Kidney Injury (AKI)

- 16% Pediatric AKI
- 20% Adult AKI (66% in the elderly)
Drug Nephrotoxicity

- Direct Tubular Injury
- Interstitial Nephritis
- Increased Autoimmunity
- Crystal Induced Obstruction
- Injury to other organs leading to secondary AKI, Rhaddomyolysis / HRS
- Impaired autoregulation
Renal Manifestations of Drug Induced Injury

**Type A ADR**
- Acute or Chronic cellular injury
  - Acute Tubular Necrosis (ATN)
  - Chronic Interstitial Nephritis
- Crystal Induced Tubular Obstruction (AKI)

**Type B ADR**
- Type I Hypersensitivity (no nephrotoxicity)
- Secondary renal injury due to idiosyncratic extra-renal complications
  - Rhabdomyolysis
- Type 4 Hypersensitivity
  - Acute Interstitial Nephritis
Examples of Type A Drug Nephrotoxicity

- Aminoglycosides (ATN)
- Amphotericin (ATN)
- Vancomycin (ATN)
- Protease Inhibitors (ATN)
- IV contrast (ATN)
- Cis Platinum (ATN)
- Bactrim (ATN)
- NNRTI (ATN)
- Foscarnet (ATN)
- Ifosfamide (ATN)
- Calcineurin inhibitors (CIN)
- Lithium (CIN)
- Colistin (ATN)
- Analgesics (CIN)
- Acyclovir (ATN)
- NSAID (CIN)
Typical Examples of Type A Drug Nephrotoxicity
Crystal Induced AKI / Stones

- Triamterene
- Ciprofloxacin
- Protease Inhibitors
- Allopurinol
- CA Inhibitors
- Guafenesin
Classification of Interstitial Nephritis

Interstitial Nephritis

Chronic

Type B ADR Acute
## Examples of Drug Induced Nephrotoxicity

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B: Acute</th>
<th>Type B: Subacute/Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 year old patient with MRSA Treated with IV Vancomycin</td>
<td>55 year old woman started on Bactrim for a UTI</td>
<td>60 year old with GERD on PPI for 3 months</td>
</tr>
<tr>
<td>Trough levels 15-20 mg/dl after 2 weeks of therapy</td>
<td>7 days later she developed a fever / rash and increased creatinine</td>
<td>Progressive rise of creatinine over weeks without any constitutional symptoms</td>
</tr>
<tr>
<td>Baseline creatinine 1.6 mg/dl (Stage 3 CKD secondary to Diabetes)</td>
<td>Urine sediment shows wbcs, rbc, granular casts</td>
<td>Urine sediment shows granular and waxy casts, wbcs, rbc</td>
</tr>
<tr>
<td>Increased creatinine to 2.4 mg/dl</td>
<td></td>
<td>Interstitial Nephritis</td>
</tr>
<tr>
<td>Urine sediment: granular casts</td>
<td></td>
<td>Interstitial Nephritis</td>
</tr>
</tbody>
</table>

**Acute Tubular Necrosis (ATN)**

**Interstitial Nephritis**
Etiology of AKI Differs by Location

Outpatient
- Pre-renal azotemia: 15%
- Acute GN: 10%
- Acute Interstitial Nephritis: 10%
- Obstructive Uropathy: 5%

Inpatient
- Pre-renal azotemia: 10%
- ATN: 20%
- Acute GN: 5%
- Acute Interstitial Nephritis: 5%

33,000 cases Annually
CKD in the U.S.
(23 million Patients)

- Interstitial Nephritis: 10%
- Unknown: 10%
- Hereditary: 5%
- Urologic: 2%
- Glomerulonephritis: 10%
- Diabetes: 39%
- HTN: 24%

[Diagram showing bar charts for different countries and regions, indicating proportions of various factors contributing to chronic kidney disease.]
Key Differential Diagnosis in Drug Induced Nephrotoxicity

Type A
ATN

- Discontinue specific drug
- Conservative Management

Type B
Interstitial Nephritis

- Discontinue specific drug
- Frequent Steroid Therapy
Etiology of Chronic Interstitial Nephritis

Acute Interstitial Nephritis (AIN)

Inadequately Treated

Chronic Interstitial Nephritis (CIN) – CKD and ESRD
AIN Experience – 1998-2013

- Sarcoid: 50%
- Sjogren’s: 25%
- TINU: 11%
- IgG4 RSD: 6%
- Infectious: 7%
- Autoimmune: 22%
- Drugs: 71%
Increasing Prevalence of Interstitial Nephritis in Patients with AKI

Rising biopsy prevalence of the Diagnosis of AIN as a cause of AKI
Increasing Incidence of AIN - UK
Increasing Prevalence of Interstitial Nephritis in all Kidney Biopsies

Rising prevalence in the Elderly

Avg age 45

Avg age 61

15-65 yrs

> 65 yrs

%
The Renal Interstitium

- What is it?
- Where is it?
- What diseases affect it?
- How do we diagnose and treat it?
What is all this open space????

This is the Interstitial Space

Gerota’s Capsule
Normal Glomerulus and Tubules:

“Back to Back “ tubular arrangement

Only 1-3 interstitial cells within any trigone

Interstitial Space
The Interstitium

Functional Characteristics

- **Structural support** of the
  - Tubules
  - Vasculature
- Conduit for solute and oxygen transfer
- Production of cytokines
- **Hormone production**
  - Prostaglandins (medulla)
  - 1-OH Hydroxylation of Vitamin D (proximal tubule)
  - Erythropoietin – cells around the peritubular capillaries
  - Renin

Caveat:
Tubular disorders are more likely associated with a higher risk of osteomalacia and anemia compared to Glomerular diseases for any given degree of renal dysfunction.
The Interstitium

Renal Interstitial Cells

- **Cortex**
  - Fibroblasts (Type I)
    - Fibronectin, **Collagen I,III,VI**, Proteoglycans
    - EPO production (peritubular capillary fibroblasts)
  - Mononuclear cells (MHC class II) - Myeloid origin / Dendritic
- **Medulla**
  - Fibroblasts
  - Mononuclear cells (MHC class II)
  - Pericytes
  - Lipid-laden cells (PG production)
  - Pluripotent stem cells (?)
Classification of Interstitial Nephritis

Interstitial Nephritis

Chronic

Acute

Drug Induced

Infectious

Immune

Snake and Insect Bites

Metabolic Uric acid and Oxalate

Neoplasia
AIN Experience – 1998-2013

- Sarcoid: 50%
- Sjogren’s: 25%
- TINU: 11%
- IgG4 RSD: 6%

- Infectious: 7%

- Antibiotics: 50%
  - PPI: 27%
  - NSAIDS: 21%

- Non-Antibiotics: 50%

- Autoimmune: 22%
Acute Interstitial Nephritis
Common Drugs

- PPI – all classes of proton pump inhibitors
- NSAIDs
  - Both COX-1 and COX-2 inhibitors
- Allopurinol
- Ampicillin / PCN
- Cephalosporin
- Rifampin
- Sulfonamides
  - Furosemide
  - Bumetanide
  - Trimethoprim-Sulfamethoxazole
- Ciprofloxacin

Non-Abx Drugs

If you are sulfa allergic you may need to avoid all loop diuretics except Ethacrynic acid
Pathogenesis of Acute Interstitial Nephritis

**Type I Hypersensitivity Reaction**
- Immediate (minutes)
- IgE
- Systemic Vasoactive Mediators
- Anaphylaxis

**Type IV Hypersensitivity Reaction**
- Delayed (days-months)
- Cell Mediated: T cells
Drug Induced Acute Allergic Interstitial Nephritis

- Characterized by predominant involvement of the renal interstitial compartment by
  - Interstitial edema
  - Interstitial cellular infiltrate
    - T lymphocytes (70%- both CD4 and CD8)
    - Monocytes (15%)
    - Eosinophils (variable based on drug compound)
    - B cells (7%)
    - Neutrophils
    - Granuloma formation
Acute Interstitial Nephritis = ATN + Cellular Infiltrate

Infiltrate are **CD4+ and CD8+ T cells** followed by macrophages /eosinophils with **very, very rare plasma cells**:

Type IV Hypersensitivity reaction

Tubulitis = infiltration of the tubules by T lymphocytes
Acute Interstitial Nephritis

Tissue Eosinophils
Adverse Drug Reaction (ADR) : Drug Hypersensitivity Reaction (DHR)

1. Altered immunogenicity of normal tissue by the drug
2. Development of antibodies to the drug (immune complexes)
3. P-I concept: Pharmacologic Interaction of the drug with immune HLA receptors
4. Metabolism of the drug into immunogenic substances (proximal tubule)
5. Haptenization: binding of the drug to self proteins that become immunogenic and trapped in local tissues (kidney)
Drug Induced AIN: Structure Matters!

- All drugs that share a common “backbone” or “core structure” elicit the same risk of AIN
Acute Allergic Interstitial Nephritis

- Acute rise in creatinine temporally related to an offending drug
  - 5 - 7 Days to months
- Constellation of clinical findings include:
  - Fever (20%)
  - Rash (30%)
  - Eosinophilia (30%)
  - Eosinophiluria
  - Non-nephrotic range proteinuria
    - < 2 gm
  - Combination of Type I, Type II and Type IV RTA
- Back (flank) pain secondary to distention of the renal capsule from cell infiltration and swelling – 30%
Types of Skin Rash seen in AIN

- Maculopapular / Morbilliform
- Diffuse Erythroderma (Exfoliative Dermatitis)
- Toxic Epidermal Necrolysis
Urinalysis in AIN

- Normal sediment: 24%
- Microscopic hematuria: 39%
- Pyuria: 26%
- Gross hematuria: 6%
- Cylinduria: 3%
- Telescopic urine: 2%
Urinalysis in AIN = **Tubulo-Interstitial Nephritis** (ATN + Inflammation)

- **Granular Casts**
- **RBCs including Dysmorphic RBCs**
- **WBCs**

- **Rare RBC Casts**
- **WBC Casts (50%)**
- **Renal Tubular Epithelial cells**
- **Eosinophils**
Urinalysis in AIN

- Urinary WBCs are an under-appreciated manifestation of AIN
- Often confused with a UTI, the diagnosis of AIN may be delayed by prolonged antibiotic treatment even in the presence of a negative urine culture
- WBCs and WBC casts in the presence of AKI and a negative culture strongly suggests AIN
Differential Diagnosis of Eosinophiluria

- AIN
- Cholesterol emboli
- Acute / chronic cystitis
- UTI / prostatitis
- Transplant rejection

**Hansel’s Stain**: Previously Recommended Predictor if

\[>1\% \text{ of urinary wbc} = \text{ eosinophils}\]

- However based on this data
- Urinary eosinophils should no longer be used as a biomarker for ATIN.
Imaging in AIN

U/S
• Increased echogenicity
• Increased size

Gallium
• $^{67}$gallium binds to lactoferrin, which is expressed on inflammatory cell surfaces and also released by leukocytes within the kidney interstitium
• Increased uptake

PET
• Uptake of 2-[18F] fluoro-2-deoxy-D-glucose by infiltrating inflammatory cells
Interstitial Nephritis: Proteinuria

Nephrotic Range Proteinuria: 2.5%

Non Nephrotic Range Proteinuria: 97.5%
**AIN and NSAID’s**

Lack the typical features of AIN

- Prolonged use 3-6 months
- Absence of fever, rash, eosinophilia
- Lower concentration of infiltrating eosinophils on biopsy

Association with **Minimal Change** or **Membranous Nephropathy**
The World of NSAID Induced Renal Disease

- Pre-Renal Azotemia
- Electrolytes: Hyperkalemia, Hyponatremia
- Acute Interstitial Nephritis
- Membranous Nephropathy
- Chronic Interstitial Nephritis
- Papillary Necrosis
- Minimal Change Disease
Drug Induced AIN and Nephrotic Syndrome

- NSAIDs
- Interferon
### Differentiating ATN from AIN

<table>
<thead>
<tr>
<th></th>
<th>ATN</th>
<th>AIN</th>
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<tbody>
<tr>
<td><strong>Time of onset</strong></td>
<td>Days to weeks</td>
<td>Weeks to months</td>
</tr>
<tr>
<td><strong>Kidney U/S</strong></td>
<td>Normal</td>
<td>Large / Echogenic</td>
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<tr>
<td><strong>Systemic Findings</strong></td>
<td>None</td>
<td>Rash/fever</td>
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<tr>
<td>**Eosinophilia/</td>
<td>None</td>
<td>Occasional</td>
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<tr>
<td>Eosinophiluria**</td>
<td></td>
<td></td>
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<tr>
<td><strong>Potassium</strong></td>
<td>Elevated in proportion to GFR</td>
<td>Disproportionately elevated to GFR</td>
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<tr>
<td></td>
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<td>(Type IV RTA)</td>
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<tr>
<td><strong>FENA</strong></td>
<td>&gt; 2%</td>
<td>&gt; 2%</td>
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<tr>
<td><strong>Acidosis</strong></td>
<td>Anion Gap</td>
<td>Non Anion Gap</td>
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<tr>
<td><strong>Urinalysis</strong></td>
<td>Granular Casts</td>
<td>Granular Casts</td>
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<tr>
<td></td>
<td>Renal Tubular Cells</td>
<td>WBC casts</td>
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<tr>
<td></td>
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<td>WBCs, RBCs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rare RBC casts</td>
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</tbody>
</table>
**PPI use in the U.S.**

- 15 million users a year
- $10 Billion dollars

40-70% of these prescriptions have no appropriate indication
25% of Users can discontinue the medication with no relapse

*JAMA Intern Med*. 2016 Feb;176(2):238-46
PPI Use and Systemic Complications: Causal Associations

- Hypo-Magnesemia
- Fractures
- C. Diff Colitis
- AKI
- CKD
- Dementia
PPI use in the Atherosclerotic Risk Trial over 13 Years Followup

JAMA Intern Med. 2016 Feb;176(2):238-46
Increasing Incidence of AIN - UK

Etiology of AIN
Antibiotics 35%
PPI 35%
NSAIDs 20%
Risk of AKI with PPI Use in 2 Major Population Studies

Atherosclerotic risk Trial

<table>
<thead>
<tr>
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<th>Overall Population</th>
<th>Baseline PPI Users</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>No. of Participants</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>326</td>
<td>5617</td>
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<tr>
<td>Old</td>
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<td>Race</td>
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<td>White</td>
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<td>Black</td>
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<tr>
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<td>ACE-I/ARB use</td>
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<td>734</td>
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<td>226</td>
<td>157</td>
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<td>Diuretics use</td>
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<tr>
<td>No</td>
<td>777</td>
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<td>Overall</td>
<td>960</td>
<td>11145</td>
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Geisinger Health System

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<th>Baseline PPI Users</th>
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<td>226879</td>
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<tr>
<td>Yes</td>
<td>1608</td>
<td>21872</td>
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<tr>
<td>Overall</td>
<td>10176</td>
<td>248751</td>
</tr>
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</table>

Increased Risk of 70% for AKI in PPI users

JAMA Intern Med. 2016 Feb;176(2):238-46
PPI Compared to H2 blockers and the risk of CKD: VA Study

Duration of PPI exposure and risk of renal outcomes

- Incident eGFR < 60 ml/min/1.73m2
- Incident chronic kidney disease
- Doubling of serum creatinine
- Greater than 30% decline in eGFR
- End stage renal disease
- End stage renal disease or > 50% decline in eGFR

Hazard Ratio

Cumulative exposure in days

≤30  31-90  91-180  181-360  361-720  >720
Risk of CKD: VA Study

N = 23,000

Arora P, BMC Nephrology. 2016;17:112
PPI and Allergic Interstitial Nephritis

Any Patient on a PPI with AKI: Suspect the PPI!!!
Persistent CKD after AKI from PPI

Conclusion
Patients with AKI from PPI often are left with persistent CKD due to delayed diagnosis.
AIN & Proton Pump Inhibitors

- Idiosyncratic (no relation to dose/duration)
  - All drug classes implicated
- Minimal systemic hypersensitivity reaction
  - Fever <50%
  - Rash <10%
  - Eosinophilia < 10%
- Duration of PPI treatment prior to AIN
  - Mean 10 weeks (range 1 wk – 18 months)
- Path: AIN, tissue eosinophils seen in approx 80%
- Treatment often delayed
  - 75% of cases have been left with Stage 3-4 CKD

TH17/TH1 response >> TH2 response
(atypical of most cases of drug induced AIN)
## Proton Pump Inhibitors and Kidney Disease—GI Upset for the Nephrologist?

Stephanie M. Toth-Manikowski\(^1\) and Morgan E. Grams\(^{1,2}\)

\(^1\)Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA; and \(^2\)Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Type of kidney injury evaluated</th>
<th>Reference group</th>
<th>Risk associations with PPI use</th>
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<tbody>
<tr>
<td>Geevasinga et al., 2006(^{36})</td>
<td>Case series</td>
<td>AIN</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Simpson et al., 2006(^{37})</td>
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<td>Leonard et al., 2012(^{38})</td>
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<td>AIN</td>
<td>No PPI use</td>
<td>OR 3.20 (0.80–12.79)</td>
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<td>OR 1.06 (0.97–1.14)</td>
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<td>Antoniou et al., 2015(^{41})</td>
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<td>AKI</td>
<td>No PPI use</td>
<td>HR 2.52 (2.27–2.79)</td>
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<td>Prospective cohort</td>
<td>AKI</td>
<td>No PPI use</td>
<td>HR 1.64 (1.22–2.21)</td>
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<td>AKI</td>
<td>H(_2)RA use</td>
<td>HR 1.31 (1.22–1.42)</td>
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<td>Lazarus et al., 2016(^{44})</td>
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<td>AKI</td>
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<td>HR 1.58 (1.05–2.40)</td>
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<td>H(_2)RA use</td>
<td>HR 1.50 (1.14–1.96)</td>
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<td>Lazarus et al., 2016(^{46})</td>
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<td>AKI</td>
<td>No PPI use</td>
<td>HR 1.17 (1.12–1.23)</td>
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<td>No PPI use</td>
<td>HR 1.39 (1.01–1.91)</td>
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<td>H(_2)RA use</td>
<td>HR 1.29 (1.19–1.40)</td>
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<td>Xie et al., 2016(^{49})</td>
<td>Prospective cohort</td>
<td>CKD</td>
<td>H(_2)RA use</td>
<td>HR 1.28 (1.23–1.34)</td>
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</tr>
<tr>
<td>Peng et al., 2016(^{51})</td>
<td>Case-control</td>
<td>ESRD</td>
<td>No PPI use</td>
<td>OR 1.88 (1.71–2.06)</td>
</tr>
</tbody>
</table>
Risk of AIN/AKI and CIN/CKD with PPI

AKI
OR 2.78

CKD
OR 1.47
The Atherosclerosis Risk in Communities (ARIC) study found that magnesium level of \( \leq 0.7 \text{ mmol/L} \ (\leq 1.8 \text{ mg/dL}) \) was associated with incident CKD and endstage renal disease (ESRD).
5 – Aminosalicylates

- AIN has been reported with all preparations used for inflammatory bowel disease
  - Asacol®
  - Pentasa®
  - Dipentum®
  - Colazal®
- idiosyncratic, non-dose-dependent reaction
- 40% incidence of CKD as a result of delayed recognition and cessation of drug exposure
HAART Related Nephropathy

- **Protease Inhibitors**
  - Indinavir / Atazanavir
    - Crystalluria / AKI / Nephrolithiasis
    - Less frequent with other PI
    - Additional causes of crystalluria in HIV patients
      - Ciprofloxacin
      - Acyclovir
      - Sulfadiazine
- **Allergic Interstitial Nephritis**
<table>
<thead>
<tr>
<th>Checkpoint Inhibitors</th>
<th>Ifosfamide</th>
<th>Pemetrexed</th>
<th>Intravesicle BCG</th>
</tr>
</thead>
</table>
| pembrolizumab and nivolumab that target PD-L1, atezolizumab, which is a PD-L1 inhibitor, and ipilimumab, which binds to CTLA-4. | • Alkylation agent  
• Predominant ATN with predilection for the proximal tubule – Fanconi’s syndrome  
• AIN reported in 30% of cases | • enzymes involved in DNA synthesis and is used in the treatment of mesothelioma and non-small cell lung cancer  
• Antifolate  
• Predilection for the proximal tubule | • live attenuated vaccine, is an established and effective treatment for noninvasive transitional cell carcinoma of the bladder  
• Leads to Type IV hypersensitivity reaction and AIN |
| Frequent autoimmune sequelae  
AIN develops 2 wks to 8 months AFTER initiation of therapy and 2 months after the last dose  
• Steroid responsive | | | |
Renal Biopsy for Drug Induced AIN

AKI Secondary to ATN

Suspected AIN

Goal of Therapy in AIN

Fibrosis begins after 7 days!!

Trichrome stain often used to demonstrate Fibrosis
Outcome of AIN

Complete Recovery 50%

Residual CKD 50%

10% ESRD

Bhaumik SK. Ren Fail. 1996;18(1):97
Outcome of AIN based on Etiology

- Antibiotic: Complete 53, Partial 41, None 6
- PPI: Complete 40, Partial 40, None 20
- NSAIDs: Complete 42, Partial 16, None 42
- Autoimmune: Complete 60, Partial 30, None 10
Early Steroid Rx improves Recovery of Renal function in drug induced AIN

<table>
<thead>
<tr>
<th>Std Rx - Recovery</th>
<th>Complete</th>
<th>Incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from drug withdrawal to RX (days)</td>
<td>13 +/-10</td>
<td>34 +/-17</td>
</tr>
</tbody>
</table>

Interstitial Fibrosis

- Mild: 89% (29%)
- Mod: 11% (46%)
- Severe: 0% (25%)

Drug Induced AIN: To Steroid or not to Steroid?

Overall patients receiving steroids have improved renal function at short and long term followup compared to patients without therapy.

Table 1. Studies examining corticosteroid therapy in acute interstitial nephritis

<table>
<thead>
<tr>
<th>Author, Yr (ref)</th>
<th>Sample size</th>
<th>Peak SCr, mg/dl</th>
<th>Final SCr, mg/dl</th>
<th>Follow-Up, Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid</td>
<td>No Steroid</td>
<td>Steroid</td>
<td>No Steroid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steroid</td>
<td>No Steroid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steroid</td>
<td>No Steroid</td>
</tr>
</tbody>
</table>
| Clarkson et al. 2004 (4) | 26 | 16 | 7.9 | 6.1 | 1.6 | 1.6 | 12 | Patients received steroids late after diagnosis (median delay >3 wk). Steroid treated patients with complete recovery had shorter delay to steroids (13 d) as compared with those without complete recovery (34 d).
| González et al. 2008 (5) | 52 | 9 | 5.9 | 4.9 | 2.1 | 3.7 | 19 |
| Raza et al. 2012 (7) | 37 | 12 | 6.5 | 5.2 | 2.8 | 3.4 | 19 |
| Muriithi et al. 2014 (6) | 83 | 12 | 3.0 | 4.5 | 1.4 | 1.5 | 6 |
| Valluri et al. 2015 (8) | 73 | 51 | 4.03 | 3.16 | NR | NR | 12 |
| Predecki et al. 2016 (9) | 158 | 29 | 20.5 ml/min (eGFR) | 25 ml/min (eGFR) | 43 ml/min (eGFR) | 24 ml/min (eGFR) | 24 |

SCr, serum creatinine concentration; NR, not reported.
Steroid Therapy for AIN
Significant Benefit on the Development of CKD

Improved Renal Outcome with Steroid Therapy in AIN

Steroid treated patients experienced a greater degree of renal recovery.

Patients with AIN due to PPI had a lower response rate to steroids.
Drug Induced AIN: When to Biopsy?

Possible DI-AIN?
- Identify and withdraw the offending agent(s)
- Supportive care and monitoring kidney function over next 3-5 days
  - Kidney function improving:
    - Continue monitoring
  - Kidney function not improving or worsening:
    - Kidney biopsy
    - Other diagnosis:
      - Treat underlying disease process
  - AIN with > 75% IF:
    - AIN with < 75% IF:
      - Contraindication to steroid use?
        - No: Corticosteroids
        - Yes: Other agents

- AKI, AKD, or rapidly progressive CKD of unclear etiology
- Sterile pyuria or urinary WBC casts
- Eosinophilia and/or rash
- Patient received drug associated with AIN

250–500mg intravenous methylprednisolone followed by 1 mg/kg per day of oral prednisone or 1 mg/kg per day of oral prednisone without intravenous therapy

Continue for 6 weeks – if no improvement – then discontinue

In steroid intolerant patients, mycophenolate mofetil can be considered
Treatment of Drug Induced AIN

- Immediate discontinuation of the offending agent
- No improvement within 5-7 days or Dialysis dependence
- Glucocorticoid Therapy
Etiology of Chronic Interstitial Nephritis

Acute Interstitial Nephritis (AIN)

Chronic Interstitial Nephritis (CIN)
Classification of Interstitial Nephritis

- Interstitial Nephritis
  - Acute
    - Genetic/Metabolic
  - Chronic
    - Secondary to Primary Glomerular Diseases
    - Direct Drug Induced without Acute Interstitial Nephritis
    - Metabolic Calcium/Uric Acid / Hypokalemia
    - Neoplasia
      - Analgesic Therapy
      - Calcineurin Inhibitors
      - Lithium
      - Aristolochic Acid (Herbal)
      - Heavy Metals
      - Mycotoxins
Chronic Interstitial Nephritis: Analgesic Nephropathy

- Most common drugs worldwide responsible for chronic interstitial fibrosis
- Primary analgesic use involves combination therapy of
  - Phenacetin ± Acetaminophen (metabolite)
    And
  - ASA or Caffeine
  - NSAIDS may be able to induce the same syndrome independently
**Chronic Interstitial Nephritis: Analgesic Nephropathy**

- **Dose dependent**
  - Years of chronic use
  - Cumulative dose of 3 kg of index compound
  - Daily ingestion of 1 g/day over 3 years

- **Pathogenesis**
  - Intra-renal conversion to reactive metabolites
  - Enhanced concentration in the medulla/papillae
Papillary Necrosis
Blunting of the Calyces
Calcified Papillae
Small contracted kidneys
Papillary Necrosis
Lithium and the Kidney

- Nephrogenic DI (20-40%)
- Type I distal RTA
- Chronic Interstitial Nephritis (15-20%)
- Hypercalcemia (Hyperparathyroidism – direct effect on the gland)

Lithium enters the tubules through the Na channel of the collecting ducts (ENAC) in the principal cells.

Prevention of nephrotoxicity can be accomplished with the concomitant use of amiloride.
Summary: Drug Nephrotoxicity

Interstitial Nephritis is a Type B ADR represents an important cause of both AKI and CKD in the outpatient and inpatient population and is increasing in frequency.

Acute interstitial nephritis (AIN) from PPI often leads to CKD as a result of delayed diagnosis and lacks the typical clinical presentation of AIN.

Early discontinuation of the offending drug and possibly the use of steroids may reduce the risk of CKD in drug-induced AIN.

Chronic interstitial nephritis (CIN) often results from poorly treated AIN but also may develop directly without preceding AIN.

Analgesic Nephropathy and Lithium represent two typical causes of CIN.

Drug-induced nephrotoxicity represents a serious consequence of ADR: careful review of the medication list is essential in all patients with AKI or CKD.
Drug Induced Nephrotoxicity
Mechanisms of Drug Induced AIN

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Illustration</th>
<th>Published Drugs Linked to AIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hapten</td>
<td><img src="image" alt="Hapten Illustration" /></td>
<td>Penicillins&lt;sup&gt;1,46&lt;/sup&gt;: Amoxicillin, Ampicillin, Dicloxacillin, Oxacillin, Benzy1penicillin, Carbencillin, Cloxacillin, Flucloxacillin, Methicillin, Piperacillin/Tazobactam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cephalosporins&lt;sup&gt;1,46&lt;/sup&gt;: Cefaclor, Cefepime Cefamandole, Cefazolin, Cefoperazone, Cefotaxime, Cefotetan, Cefoxitin, Ceftriaxone, Cephalexin, Cephaloridine, Cephalothin, Cephradine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAIDs Including Salicylates&lt;sup&gt;1,47&lt;/sup&gt;: Acetaminophen, Alclofenac Aspirin, Diclofenac, Naproxen</td>
</tr>
<tr>
<td>Pro-hapten</td>
<td><img src="image" alt="Pro-hapten Illustration" /></td>
<td>Sulfonamide-Containing Drugs&lt;sup&gt;1,8,48-50&lt;/sup&gt;: Celecoxib, Chlorthalidone, Chlorpropamide, Furosemide (Furosine), Hydrochlorothiazide, Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>p-i Concept</td>
<td><img src="image" alt="p-i Concept Illustration" /></td>
<td>Other&lt;sup&gt;1,6,7,51&lt;/sup&gt;: Carbamazepine (HLA-B&lt;sup&gt;*15:02&lt;/sup&gt;), Allopurinol (HLA-B&lt;sup&gt;*58:01&lt;/sup&gt;, HLA-B&lt;sup&gt;*58:01&lt;/sup&gt;, Flucloxacillin (HLA-B&lt;sup&gt;*57:01&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>

Abbreviations: ◊ Drug (as hapten); ○ carrier protein; □ nonreactive drug metabolized into a reactive compound that binds to specific proteins (haptenization); APC, antigen-presenting cell; ⊙ host-specific T-cell receptor; MHC, major histocompatibility complex protein expressed by host.
Drug Induced – AIN:
Major role of the Proximal Tubule

High blood flow of the kidney predisposed it to increase delivery of drugs.

Filtration / secretion of the drug with subsequent absorption / metabolism by the proximal tubule.

3 phases:
“antigen recognition” and presentation phase
an “integrative” or regulatory (primarily cellular) phase
an “effector” or mediator (primarily humoral) phase.
Tubulointerstitial Injury is the Final Common Pathway to CKD/ESRD in Glomerular and Interstitial Diseases

The mal-adaptive repair of injured proximal and distal tubular cells from any process leads to progressive interstitial fibrosis –

Caveat: The prognosis of any kidney disease is dependent on the degree of tubulointerstitial injury (not the degree of glomerular disease)
Location of Chemotherapy Induced Nephrotoxicity