AIN and CIN for the Boards

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Outline

• Background on and Prevalence of AIN: What is AIN and is it common?
• Etiology of AIN: Common causes
• AIN as a clinical syndrome: How does it present?
• Diagnosis of AIN: What tests are useful?
• Treatment of and Outcomes after AIN: What works and is CKD a problem?
• Review of various AIN/CIN etiologies

Acute Interstitial Nephritis (AIN)

Definition

• AIN can be part of a systemic allergic syndrome with multiple organ involvement
• AIN can be an isolated renal syndrome characterized histologically by an inflammatory process involving the renal interstitium and tubules
• AIN may be caused by a variety of etiologies, which have changed over time

<table>
<thead>
<tr>
<th>Tubular, Interstitial and Cystic Disorders</th>
<th>Approximate % of Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal tubular disorders and Fanconi's syndrome – which may include:</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Drug induced</td>
<td></td>
</tr>
<tr>
<td>Crystal deposition</td>
<td></td>
</tr>
<tr>
<td>Genetic</td>
<td></td>
</tr>
<tr>
<td>Tubulointerstitial nephritis – which may include:</td>
<td>2%</td>
</tr>
<tr>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>Renal cystic disease – which may include:</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>ADPKD</td>
<td></td>
</tr>
<tr>
<td>Renal mass – which may include:</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Cystic</td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td></td>
</tr>
</tbody>
</table>
Which of the following most closely reflects the overall prevalence of biopsy-proven AIN?

A. 2-5%
B. 5-10%
C. 10-15%
D. 15-20%
E. > 20%

Acute Interstitial Nephritis (AIN)

**Historical Background**

Councilman (1898)
‘Sterile’ interstitial nephritis in patients with ARF dying from scarlet fever and diphtheria

Kimmelstiel & Kannestein (1942)
‘Allergic’ interstitial nephritis associated with bacterial sepsis

More et al. (1946)
Interstitial nephritis from pharmaceutical drugs (sulfonamide allergy)

Klassen & others (1971-1974)
Interstitial nephritis from autoimmune-mediated processes

Nielson & coworkers (1980s)
Tubulointerstitial antigens, nephritogenic T cells, and fibrogenic processes of AIN

Prevalence of AIN

Table 1. Incidence of AIN in published kidney biopsy registries

<table>
<thead>
<tr>
<th>Year (ref)</th>
<th>Period</th>
<th>Biopsies (country)</th>
<th>ARF cases</th>
<th>AIN cases</th>
<th>%AIN of ARF</th>
<th>% AIN of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960 [1]</td>
<td>1970-1980</td>
<td>M 1960 UK</td>
<td>1,600</td>
<td>51</td>
<td>3.2%</td>
<td>0.95%</td>
</tr>
<tr>
<td>1968 [2]</td>
<td>1978-1980</td>
<td>M 1968 UK</td>
<td>1,067</td>
<td>14</td>
<td>1.3%</td>
<td>0.20%</td>
</tr>
<tr>
<td>1968 [3]</td>
<td>1978-1984</td>
<td>M 1968 UK</td>
<td>1,024</td>
<td>10</td>
<td>1.0%</td>
<td>0.10%</td>
</tr>
<tr>
<td>1978 [4]</td>
<td>1984-1990</td>
<td>M 1978 UK</td>
<td>693</td>
<td>9</td>
<td>1.3%</td>
<td>0.01%</td>
</tr>
<tr>
<td>2000 [5]</td>
<td>1984-2000</td>
<td>M 1984 UK</td>
<td>645</td>
<td>9</td>
<td>1.4%</td>
<td>0.01%</td>
</tr>
<tr>
<td>2002 [6]</td>
<td>1990-2002</td>
<td>M 1990 UK</td>
<td>610</td>
<td>9</td>
<td>1.5%</td>
<td>0.01%</td>
</tr>
<tr>
<td>2002 [7]</td>
<td>1990-2004</td>
<td>M 1990 UK</td>
<td>605</td>
<td>9</td>
<td>1.5%</td>
<td>0.01%</td>
</tr>
<tr>
<td>2007 [8]</td>
<td>1997-2004</td>
<td>M 1997 UK</td>
<td>306</td>
<td>9</td>
<td>3.0%</td>
<td>0.01%</td>
</tr>
<tr>
<td>2009 [9]</td>
<td>1999-2004</td>
<td>M 1999 UK</td>
<td>293</td>
<td>9</td>
<td>3.1%</td>
<td>0.01%</td>
</tr>
</tbody>
</table>

Board Question

Which of the following most closely reflects the prevalence of biopsy-proven AIN in patients with AKI?

A. 5-10%
B. 10-15%
C. 15-20%
D. 20-30%
E. > 30%
Is AIN common in unexplained AKI?

• 109 consecutive biopsies at St. Bartholomew’s Hospital in England between 1978 and 1985
• Unexplained AKI and normal sized kidneys on ultrasound
• 29 patients (27%) had AIN, the most common cause of AKI

Is AIN common in AKI?

<table>
<thead>
<tr>
<th>Year</th>
<th>Biopsy Proven AIN</th>
<th>Pre-1990s</th>
<th>10% – 19%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964-1974</td>
<td>10.7% (9/84)</td>
<td>1966-1977</td>
<td>14% (29/209)</td>
</tr>
<tr>
<td>1978-1985</td>
<td>27% (29/109)</td>
<td>1988-2001</td>
<td>10.3% (60/583)</td>
</tr>
<tr>
<td>1994-2009</td>
<td>13% (392/3059)</td>
<td>1994-2000</td>
<td>18% (60/330)</td>
</tr>
</tbody>
</table>


Board Question
Which of the following is the most common cause of AIN?

A. Sarcoidosis
B. Tubulointerstitial nephritis with uveitis (TINU)
C. Medications
D. Infectious agents
E. Sjogren syndrome
F. IgG4 disease

Board Question
Which class of drugs is most commonly associated with AIN?

A. Proton pump inhibitors
B. NSAIDs
C. Antimicrobials
D. Anticonvulsants
E. H₂ antagonists
F. Chemotherapeutic agents

Causes of AIN

- Infectious Agents
  - Indirect Infection: Bacteria, Viruses, Rickettsia
  - Direct Infection: Pyelonephritis, XGP, Malacoplakia
- Systemic Diseases
  - Sarcoidosis, Sjogren's Syndrome, SLE, HIV, IgG4
- Idiopathic
  - TIN-Uveitis Syndrome
  - Anti-TBM Disease
- Drugs (>70%)
  - β-lactams, sulfonamides, NSAIDs, PPIs, rifampin, dilantin, allopurinol, H₂ Blockers, COX-2 inhibitors, HAART, quinolones, anti-angiogenesis drugs, and many other drugs

Drug-induced AIN

- Most common Medications

<table>
<thead>
<tr>
<th>Cause of AIN</th>
<th>β-Lactams/Sulfos</th>
<th>NSAIDs</th>
<th>PPIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960s-1980s</td>
<td>&gt;80%</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>1988-2001</td>
<td>70%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>1975-2006</td>
<td>1%</td>
<td>56%</td>
<td>37%</td>
</tr>
<tr>
<td>1994-2011</td>
<td>3%</td>
<td>44%</td>
<td>33%</td>
</tr>
<tr>
<td>1997-2011</td>
<td>11%</td>
<td>41%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Acute Interstitial Nephritis

Focus on Drug-Induced AIN

- Retrospective case review (1993-2003) in Australia
  - 18/28 (64%) cases of biopsy-proven AIN with PPI use
- Retrospective case review (2002-2005) in Auckland, New Zealand
  - 15/27 (7.7%) cases of AIN were associated with PPI use
- TGA data registry review (1991-2004)
  - 34 cases of biopsy-proven AIN associated with multiple PPIs
  - 10 cases of suspected interstitial nephritis with multiple PPIs

AIN Proton Pump Inhibitors (PPIs)

- AIN associated with omeprazole and other PPIs
  - First case of biopsy-proven AIN described with omeprazole (1992)
  - Subsequent reports of AIN associated with omeprazole (n=29, 23 biopsied) appeared in the literature over the next 12 years
  - In 2004, biopsy proven AIN from other PPIs
    - Lansoprazole, pantoprazole, rabeprazole, esomeprazole
- Retrospective case review (1993-2003) in Australia
- Retrospective case review (2002-2005) in Auckland, New Zealand
- TGA data registry review (1991-2004)

References:
2) Simpson et al. Nephrology, 2006
3) Praga et al. NDT, 2014
4) Gonzalez et al. KI, 2008
5) Clarkson et al. NDT, 2004
6) Raza et al. Nephrol 2012
7) Muriithi et al. CJASN, 2013
8) Fogazzi et al. AJKD, 2012
9) Maruthi et al. CMAJ, 2016
10) Figgis et al. AJO. 2012

Praga et al. NDT, 2014
**AIN**

**Proton Pump Inhibitors (PPIs)**

- Centre for Adverse Reactions Monitoring (CARM) data registry review (New Zealand)¹
  - 110 cases of "drug-induced AIN" associated with PPIs
    - 35 (32%) due to PPIs, 24 (22%) due to NSAIDs, 25 (23%) due to antibiotics, 6 (5%) due to diuretics
- WHO Collaborating Centre on International Drug Monitoring (Uppsala, Sweden)²
  - Databank contains more than 3.7 million spontaneous reports of adverse drug reactions from > 80 countries
  - 150 reports of PPI-associated AIN
    - Omeprazole (n=109), Lansoprazole (n=18), Pantoprazole (n=15), Rabeprazole (n=10), Esomeprazole n=(7)

1) Simpson et al, Nephrology, 2006  

**Clinical/Laboratory Manifestations**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Hem</th>
<th>Pyr</th>
<th>AKI</th>
<th>Pro</th>
<th>Eos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin*</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Other drugs*</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>PPIs*</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Geevasinga et al, Clin Gastro Hep, 2006**  
§§§§ Data from other cases

**Proton Pump Inhibitors (PPIs)**

- 5-aminosalicylate (5-AS) therapy
  - Include sulfasalazine, mesalamine, an olsalazine
  - Used for treatment of IBD (Crohn disease and ulcerative colitis)
- AIN associated with 5-aminosalicylates
  - AEse→ fever/rash (10%), idiosyncratic multi-organ hypersensitivity
  - Incidence of renal failure is 1 in 200 to 500 exposures
  - In Crohn disease, 19% of biopsies had AIN, > 50% exposed to 5-AS
- Approach to AIN associated with 5-aminosalicylates
  - Published reports of renal biopsy findings—42/44 were AIN
  - AIN develops primarily within the first year of exposure
  - Drug withdrawal, steroid therapy (best results if early)
  - Still significant CKD occurs in many patients (CIN)

Geevasinga et al, Clin Gastro Hep, 2006  
Simpson et al, Nephrology, 2006  
Perazella MA, Markowitz GS. Nat Rev Nephrol, 2010; Ambrozic JA, et al. CARM 2014
A 59 yo woman presents with fever, weight loss, and fatigue for several weeks duration despite broad spectrum antibiotics. Exam reveals diffuse rash and palpable adenopathy. Severe eosinophilia and AKI are noted. U/A has 2+ proteinuria, 1+ LE. Urine microscopy reveals 6-10 WBCs and 1-5 RBCs/HPF and 2-3 WBC casts/LPF. She undergoes PET scan for concerns over malignancy. A kidney biopsy is also performed.

**Board Question**

What is the likely cause of this clinical presentation and kidney lesion?

A) Sarcoidosis with severe granulomatous interstitial nephritis  
B) Severe toxic kidney injury with cortical necrosis  
C) DRESS syndrome with granulomatous AIN  
D) Lymphomatous infiltration of the kidney  
E) Eosinophilic leukemia with renal infiltration

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**AIN**

**DRESS syndrome**

- **DRESS (drug rash with eosinophilia & systemic symptoms)**
  - Fever, skin rash, eosinophilia, lymphadenopathy, atypical lymphocytes, & end organ involvement—AIN, pneumonitis, hepatitis (at least 3)
  - Idiosyncratic reaction to drugs such as allopurinol, sulfonamides, phenytoin, phenobarbital, & carbamazepine (vancomycin, linezolid)
- **DRESS syndrome is potentially life-threatening**
  - Drug exposure may be brief or prolonged; syndrome progression varies
  - Fever develops first followed by skin eruption, which may progress to exfoliative dermatitis followed by end organ injury
- **Cause of DRESS syndrome**
  - Mechanism ?, malfunction of toxin processing by the lymphatic system
  - A genetic predisposition may also play a role
- **Treatment for DRESS syndrome**
  - Discontinue drug, supportive care, and systemic steroids
  - Treatment for several weeks, watch for relapse following taper

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49 yo obese woman with HTN, OA, and T2 DM presents feeling poorly over past 4-6 weeks and is noted to sCr 3.2 mg/dl. Medications include glipizide, losartan/HCTZ, naproxen, and a health store weight loss regimen (past 2 yrs). Exam is unremarkable. U/A: 1+ pro, 1+ glu, trace LE & blood. Urine microscopy: 2-5 WBCs & 1-3 RBCs/HPF, 1-2 waxy casts/LPF. Biopsy is obtained.

**Board Question**

What is the likely cause of this clinical presentation and kidney lesion?

A) Sarcoidosis with severe granulomatous interstitial nephritis  
B) Severe toxic kidney injury with cortical necrosis  
C) DRESS syndrome with granulomatous AIN  
D) Lymphomatous infiltration of the kidney  
E) Eosinophilic leukemia with renal infiltration
Board Question

Which of the following is the most likely diagnosis?

A. Weight loss regimen (Aristolochic acid) nephropathy
B. Obesity-related nephropathy
C. NSAID-induced acute interstitial nephritis
D. Diabetic nephropathy
E. HCTZ-induced acute interstitial nephritis

Aristolochic Acid Nephropathy

(Chinese Herb Nephropathy)

- Rapidly progressive interstitial nephritis → ESRD
- Caused by Chinese herbal slimming regimens containing aristolochic acid (AA)
  - Aristolochia fangchi substituted for Stephania tetrandra
  - AA DNA adducts detected in kidneys
  - Rabbit and rat models confirm same lesion with exposure to AA
- Associated with uroepithelial malignancies
- First described in Belgium, but found worldwide
- AA has also been identified as the environmental agent underlying Balkan-endemic nephropathy
  - Seeds of Aristolochia clematitis comingled with wheat grain during the annual harvest

Clinical Presentation
- Silent with no symptoms
- Rapidly progressive interstitial nephritis

Laboratory Presentation
- Abnormal BUN and serum Cr
- Bland urine sediment
- Low molecular weight proteinuria
- Enzymuria
- Fanconi syndrome

Pathology/ Histopathology
- Shrunken kidneys
- Extensive interstitial fibrosis
- Atrophy and loss of tubules
- Normal glomeruli

Treatment
- Stop AA-containing agent
- Steroids slowed progression to ESRD

NSAID Nephropathy
- AIN +/- minimal change disease (MCD)
  - Develops after months to years of exposure
  - Hypersensitivity rare
  - AKI, tubular proteinuria (nephrotic with MCD)
  - Kidney biopsy typical of AIN, but may not have eos
- CIN

Analgesic Nephropathy
- Described in patients taking drug combinations
- NSAIDs, phenacetin, caffeine
  - Develops after years of exposure (> 6 pills/day for greater than 3 years)
  - Weakness, nocturia, uremia
  - CKD, tubular proteinuria, bland sediment +/- WBCs

Image credits:
AIN/CIN
Other Drugs and Toxins

- Heavy metal exposure
  - Lead, mercury, cadmium, etc associated with AIN/CIN
  - Rare in present times, lead still causes some CIN & tubulopathy
- Anti-neoplastic agents
  - Ifosfamide, TKIs (sorafenib, sunitinib), platins, ipilimumab, and few others
- Herbal products/supplements
  - Various contaminants (heavy metals, diuretics, NSAIDs)
  - Andrographis paniculata, Aristolochia sp, pennyroyal oil, etc
- Others
  - Oxalate nephropathy (orlistat, ascorbic acid, star fruit)

Acute/Chronic Interstitial Nephritis
Infections

- Numerous infectious agents have been associated with AIN
  - Legionella, Leptospira, Streptococcus, Corynebacterium diphtheriae, Enterococcus, Escherichia coli, Yersinia, Mycobacterium tuberculosis
  - EBV, CMV, polyomavirus, adenovirus, Candida, and others
- Granulomatous AIN also noted
  - Mycobacterium, fungi (histoplasmosis, coccidiomycosis), bacteria (Brucella, Chlamydia), spirochetes (Francisella, Treponema), and parasites (Leishmania, Toxoplasma)
- AIN occurs in the setting with other end organ involvement
- AIN develops from either direct parenchymal invasion or inflammatory response within the kidneys
- Treatment
  - Treat the infection (antibiotics, antivirals, anti-fungals, etc)
  - Steroids: 1 mg/kg/d x 1 month with taper

A 71 year old woman with hypertension, COPD, CAD, ischemic CMP, anemia, and stage 3a CKD (Cr 1.2 mg/dl) was admitted with left LE cellulitis. IVFs and IV pip/tazo were administered. On day 8, the patient develops a rising serum Cr.

In this clinical setting, which of the following will be diagnostic of drug-induced AIN in this patient?

A) Urine eosinophils > 5%
B) Sterile leukocyturia and WBC casts
C) Clinical history with morbilliform rash and fever
D) Large, echogenic kidneys on renal ultrasound
E) Gallium scan positive at 48-72 hours
F) Kidney biopsy showing an inflammatory interstitial infiltrate
G) None of these tests are diagnostic of drug-induced AIN
### AIN: Diagnostic Tools

- **Clinical Suspicion**
  - Clinical Renal Syndrome
  - Fever, Rash, ...
  - Culprit Drug or Disease Process
- **Blood Tests**
  - Increased serum creatinine (AKI)
  - Leukocytosis, eosinophilia, anemia, elevated ESR, transaminits
- **Urine Studies**
  - Dipstick/low grade proteinuria
  - Pyuria, hematuria, WBC casts, other casts
  - Eosinophiluria
- **Imaging Tests**
  - Renal US/CT Scan
  - Gallium Scan
  - FDG-PET Scan
- **Kidney Biopsy**
  - Gold Standard

### AIN: Clinical Renal Syndrome

- **History of Drug Exposure**
- **Clinical Symptoms/Signs**
  - Fever, Rash, or Malaise
  - Myositis, Myalgias, or Arthralgias
  - Flank and/or Abdominal Pain
  - Nonspecific symptoms

### AIN: Examination of the Urine

#### Symptoms/Signs/Labs

<table>
<thead>
<tr>
<th>Features</th>
<th>N=121 patients with AIN (92% DAIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal failure</td>
<td>100%</td>
</tr>
<tr>
<td>Acute renal failure requiring dialysis</td>
<td>40%</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>45%</td>
</tr>
<tr>
<td>Fever</td>
<td>36%</td>
</tr>
<tr>
<td>Skin rash</td>
<td>22%</td>
</tr>
<tr>
<td>Eosinophilia (&gt; 500 eosinophils per mm³)</td>
<td>35%</td>
</tr>
</tbody>
</table>

N=121 patients with AIN (92% DAIN)

- Acute kidney injury is nearly universally present
- The triad of Fever, Rash and Eosinophilia: <5-10%

### AIN: Examination of the Urine

#### Urinalysis/Urine Dipstick

<table>
<thead>
<tr>
<th>Features</th>
<th>N=121 patients with AIN (92% DAIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microhematuria</td>
<td>67%</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>5%</td>
</tr>
<tr>
<td>Leukocyuria</td>
<td>62%</td>
</tr>
<tr>
<td>Non-nephrotic proteinuria</td>
<td>93%</td>
</tr>
<tr>
<td>Nephrotic-range proteinuria</td>
<td>2.5%</td>
</tr>
<tr>
<td>Complete nephrotic syndrome</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

- Hematuria: ~70%
- Sterile Pyuria: ~80%
- Low-grade Proteinuria: ~90%
Dipstick Hematuria: varies widely, in part due to various causes and incomplete data – ~40-50%, ranges from 20 to 80%

Dipstick Leukocyturia (LE+): also varies widely, explanation similar to hematuria – ~60-80%, ranges from 20 to 90%

Proteinuria: is typically low grade (tubular) – Dipstick with trace/1+ (sometimes negative) – Spot Pro/Cr ratio or 24 hour urine (<1 g/day) – Concomitant glomerulopathy has albuminuria


Eosinophiluria

Hansel Stain
- Nasal & bronchial eos
- Nonautomated, manual with cell counts under oil
- Granules are bright red
- 100-500 WBCs viewed
- Positive test result (>1% eos, >5% eos)

Wright Stain
- Automated/rapid
- Widely employed
- Granules are faint pink, orange, or blue
- 100-500 WBCs processed
- Positive test result (>1% eos, up to 33%)

<table>
<thead>
<tr>
<th>Pts</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corwin 65</td>
<td>8/9</td>
<td>29/56</td>
<td>UTI 12/25, GN 2/2</td>
</tr>
<tr>
<td>Nolan 92</td>
<td>10/11</td>
<td>69/81</td>
<td>ATN 6/32, Pyelonephritis 6/22</td>
</tr>
<tr>
<td>Corwin 183</td>
<td>5/8</td>
<td>150/175</td>
<td>ATN 1/25, Pr 1/39</td>
</tr>
<tr>
<td>Ruffing 51</td>
<td>6/15</td>
<td>26/36</td>
<td>GN 6/49, Pr 1/3</td>
</tr>
<tr>
<td>Total 391</td>
<td>29/43</td>
<td>284/348</td>
<td>(67%; 40-91%) (83%; 52-93%)</td>
</tr>
</tbody>
</table>

Mayo Clinic Experience (1994-2011)
566 patients with both urine eosinophil testing & kidney biopsy
- Mean age 59 years
- Men/women (n = 322/244)
- Urine eosinophils (<1, 1-5, >5%); >1% (n = 179); >5% (n = 60)

- Biopsy confirmed AIN (n = 91)
- Biopsy confirmed ATN (n = 69)
- Biopsy confirmed APGN (n = 122)

Muriithi et al. CJASN, 2013
Eosinophiluria is not adequate as a biomarker to distinguish drug-induced AIN from ATN.

**AIN: Examination of the Urine**

**Urine Sediment**

- **CELLS:** WBCs, RBCs, RTE cells, Eosinophils
- **CASTS:** WBC casts, Granular casts, RTEC casts, RBC casts (rare)
- **BLAND:** No Cellular elements or Casts

**Eosinophiluria**

- Urine Eosinophils positive in **179**/566 (32%) of all pts
  - Urine Eosinophils positive in **28**/91 (31%) of all AIN
  - Urine Eosinophils positive in **26**/73 (36%) of DAIN
  - Urine Eosinophils positive in **20**/69 (29%) of ATN

<table>
<thead>
<tr>
<th>Eosinophils (%)</th>
<th>All Causes of AIN</th>
<th>Drug-Induced AIN</th>
<th>AIN</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AI Pyelonephritis Only</td>
<td>AI Pyelonephritis Only</td>
<td>AI Pyelonephritis Only</td>
<td>AI Pyelonephritis Only</td>
</tr>
<tr>
<td>&lt;1</td>
<td>6</td>
<td>12</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>&gt;5</td>
<td>10</td>
<td>32</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>44</td>
<td>38</td>
<td>77</td>
</tr>
</tbody>
</table>

Muriithi et al. CJASN 2013
AIN: Examination of the Urine

Urine Sediment findings with AIN:

- Eosinophiluria:
  - Insensitive test with specificity and positive LR only potentially acceptable using Urine Eos >5% cutoff in setting of high pretest probability

- Urinary RBCs/WBCs:
  - Examination of the urine sediment for RBCs and WBCs is neither sensitive nor specific for AIN (sterile pyuria)

- Urinary Casts:
  - Examination of the urine sediment for WBC casts has poor sensitivity; reasonable specificity for AIN (except AGN, pyelo, pap necrosis); RBC casts noted in biopsy-proven AIN

AIN: Diagnostic Imaging

Renal Ultrasound/CT Scan

- Ultrasound demonstrates hyperechogenic cortex
- Increased kidney size (150-200% increase) noted

Not Useful for Diagnosis of AIN

AIN: Imaging Studies

Gallium scanning

- Uptake in organs is measured 48-72 hours after injection of gallium
- Based on gallium binding of lactoferrin, which is produced by leukocytes and found on their surface
- Intensity in kidney compared to the spine and graded as 0-3+ (2-3+ is considered positive)
AIN: Imaging Studies in Animals
Gallium scanning

- Sensitivity variable
  - 4 studies: sensitivities of 58%, 66%, 69%, and 100%
- Specificity also poor
  - Specificity of 50-60%
  - Can be positive in normal kidney, ATN, cancer, pyelonephritis, CIN, renal atheroemboli, glomerulonephritis, AKI with IgA nephropathy, minimal change disease


AIN: Imaging Studies
Gallium scanning

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AIN: Diagnostic Tools
Kidney Biopsy

- Glomeruli and Vasculature
  - Normal or minimal disease
- Tubules
  - Tubulitis (invasion by cells)
  - Dilated tubules with tubular cell dropout
  - Tubular apoptosis and/or necrosis
- Interstitium
  - Invasion by inflammatory cells
  - Lymphocytes (T cells), macrophages, plasma cells, PMNs, and eosinophils
  - Interstitial edema \(\rightarrow\) fibrosis

Gold Standard

Acute Interstitial Nephritis
Kidney Biopsy

Normal Tubulointerstitium Acute Interstitial Nephritis
Acute Interstitial Nephritis
Kidney Biopsy

**Board Question**

A 62-year-old man with CAD, HTN and T2 DM is hospitalized for MRSA cellulitis of the left leg. Intravenous piperacillin/tazobactam is administered. On day 12 of antibiotics, serum Cr is noted to increase to 1.9 mg/dl (baseline 1.1mg/dl). Kidney function continues to decline over the next 3 days with serum Cr increasing to 3.9 mg/dl. Urine microscopy reveals 5-10 RBCs/HPF & 15-20 WBCs/HPF. Urine Protein/Cr is 0.74. Renal U/S: bilateral 11cm echogenic kidneys without hydronephrosis. Kidney biopsy reveals patchy interstitial infiltrate consisting of lymphocytes, plasma cells, & eosinophils as well as tubulitis, consistent with AIN.

**Board Material**

**Diagnostic Tools for AIN**

- **Renal ultrasound or CT scan**
  - Large swollen kidney, increased echogenicity (U/S)
  - Not specific, useful to exclude other AKI causes

- **Renal gallium scan**
  - Based on gallium binding to lactoferrin on WBCs
  - Not sensitive or specific for AIN

- **Kidney biopsy**
  - Current gold standard for AIN
  - May be helpful in diagnosing drug-induced AIN if > 10 eosinophils/20x field plus granulomas
Board Question
In this patient, which of the following is associated with an increased likelihood that kidney function will improve following a course of steroid therapy?

A) Peak serum creatinine concentration less than 6 mg/dl
B) Patchy vs. diffuse interstitial infiltrate on kidney biopsy
C) Steroid therapy initiated within 1 week of diagnosis
D) Preserved kidney size on ultrasonography
E) Baseline GFR greater than 60 ml/min/1.73m²
F) Proteinuria less than 1 gram per day

AIN: Therapeutic Options
How does one treat AIN?

- Discontinue the Offending Agent
  - Identify culprit drug and discontinue
- Supportive Therapy
  - AKI/CKD management
  - Renal replacement therapy if required
- Steroids?
  - Methylprednisolone 1g/day (initial pulse)
  - Prednisone 1 mg/kg for period of time

Treatment of Drug-induced AIN
Steroids

- Retrospective study of 2598 renal biopsies done at one center
- 2.6% of patients had AIN (n = 67), 42 cases with adequate follow-up
- Steroids: n=26 (IV Pulse then oral); Conservative: n=16
- No difference in follow-up serum creatinine at 12 months

[Graph showing treatment outcomes]
Treatment of Drug-induced AIN

**Steroids**

- Multicenter, retrospective study of 61 pts with biopsy-proven drug-induced AIN
- Steroids given (n=52), No steroids (n=9) → “control”
- Steroid treated:
  - Lower final serum Cr (2.1 mg/dl vs. 3.7 mg/dl) P<0.001
  - Reduced RRT requirement (44% vs. 3.8%) P<0.05

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.6 ± 15.3</td>
<td>56.9 ± 15.6</td>
</tr>
<tr>
<td>Euvolemic (Y/N)</td>
<td>61/15/8</td>
<td>77/22/2</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>1.1 ± 0.2</td>
<td>1.13 ± 0.37</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.9 ± 0.26</td>
<td>1.13 ± 0.37</td>
</tr>
<tr>
<td>Duration of treatment (days)</td>
<td>13.4 ± 9.49</td>
<td>12.6 ± 9.49</td>
</tr>
<tr>
<td>Lowest Cr (mg/dl)</td>
<td>1.9 ± 0.26</td>
<td>1.93 ± 0.21</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.9 ± 0.26</td>
<td>1.8 ± 0.28</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>38.1%</td>
<td>38.1%</td>
</tr>
<tr>
<td>Probable recovery of renal function</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>Days to peak (median)</td>
<td>8 (1-31)</td>
<td>5 (1-17)</td>
</tr>
<tr>
<td>Follow-up (median)</td>
<td>10 (4-19)</td>
<td>10 (4-19)</td>
</tr>
</tbody>
</table>

- Time of steroid therapy influenced recovery of kidney function
  - Serum Cr higher with longer interval between withdrawal & steroid Rx
  - Renal Recovery: Those who recovered to baseline received steroids earlier (13 days) than those who did not recover to baseline (34 days)

- Longer interval between drug withdrawal and biopsy is associated with moderate/severe interstitial fibrosis (70.8% vs. 10.7%)

**Biopsy Timing**

- Retrospective study: N=49 biopsy-proven AIN; 67% DAIN
- All patients presented with AKI
- Steroids (n=37) for mean of 5 months; No steroids (n=12)
  - Steroid: Mean peak sCr=6.5 mg/dl (1.4-14.4 mg/dl)
  - No steroid: Mean peak sCr=5.2 mg/dl (1.8-11.7 mg/dl)
- Mean follow-up: 19 months
  - Steroid: Mean sCr=2.78 mg/dl (0.9-7.3 mg/dl); RRT (16%)
  - No steroid: Mean sCr=3.4 mg/dl (0.9-8.5 mg/dl); RRT (42%)
Treatment of Drug-induced AIN

Steroids

- **Retrospective study**: N=133 biopsy-proven AIN; 70% DAIN (n=95)
- All patients (baseline sCr 1.1 mg/dl) presented with AKI (sCr=3.8 mg/dl at biopsy) with peak sCr=4.3 mg/dl
- **Steroids** (n=83) for mean of 5 weeks; **No steroids** (n=12)
  - Steroid: Mean peak sCr=4.5 mg/dl (3.3-8.4 mg/dl)
  - No steroid: Mean peak sCr=3.0 mg/dl (1.7-4.7 mg/dl)
- **Mean follow-up**: 6 months
  - Steroid: Mean sCr=1.4 mg/dl (1.1-1.8 mg/dl); RRT (7%)
  - No steroid: Mean sCr=1.5 mg/dl (1.1-2.6 mg/dl); RRT (0%)
- **Renal recovery**
  - Associated with shorter interval from AKI to steroids (8 vs. 34.5 days) and drug withdrawal to steroids (6 vs. 14 days)

Are CKD and/or ESRD complications of AIN?

- **N=128 (3*) DAIN 71% Unknown F/U**
- **N=60 DAIN 84% 12 Mo F/U**
- **N=61 DAIN 100% 19 Mo F/U**
- **N=49 DAIN 67% 19 Mo F/U**
- **N=133 (89) DAIN 70% 6 Mo F/U**

- **eGFR**: from 65 (44-95) ml/min/1.73m² to 32 (7-85) ml/min/1.73m²

Acute/Chronic Interstitial Nephritis

- **Therapy of AIN**
  - Identify the cause-drug, infection or disease
  - Withdraw the drug or treat infection/disease

- **Steroids for AIN/drug-induced AIN**
  - Not standard of care, data are inconclusive
  - However, if asked about early steroids, likely the correct answer

- **Outcomes for AIN**
  - CKD and ESRD are both complications of AIN, whether due to drugs or other causative agent
41 year old woman presents to her PCP with slowly worsening dry cough, polyuria & generalized fatigue. She describes dry eyes, a rash on her shins and pain in her hand joints. She has been taking ibuprofen for pain. Exam is notable for dry bibasilar lung crackles, tender hepatomegaly, and erythematous rash on her shins. Labs: Na 142, K 5.3, HCO3 18, BUN 56, sCr 5.5. Urinalysis: SG 1004, 1+ pro, 1+ LE and 1+ blood. Urine microscopy: 5-10 WBCs and 3-5 RBCs/HPF, 1-3 granular casts and 0-1 WBC casts/LPF. Kidney biopsy is obtained & shown below.

**Board Question**

What is the most likely diagnosis in this clinical setting?

- A) Sjogren syndrome with AIN
- B) Sarcoidosis with AIN
- C) Tubulointerstitial nephritis and uveitis (TINU)
- D) Viral syndrome with associated AIN
- E) NSAID systemic reaction with associated AIN

**Acute/Chronic Interstitial Nephritis**

**Sarcoidosis**

- A. Granulomatous interstitial nephritis
- B. Nephrolithiasis
- C. Hypercalciuria
- D. Membranous glomerulonephritis
- E. Minimal change nephropathy
Acute/Chronic Interstitial Nephritis

Sarcoidosis

• Hypercalcemia (10%)
• Hypercalciuria (50%)
  − nephrolithiasis
  − medullary calcifications
  − nephrocalcinosis

Mahevas et al Medicine, 2009; Joss et al. CJASN, 2007

• Acute (AIN) and/or chronic interstitial nephritis (CIN)
• Diffuse lymphocytic infiltrate (T cells)
• Sometimes with granulomas (giant cells)
• Occurs subclinically in anywhere from 7-27% (autopsy)

Mahevas et al Medicine, 2009; Joss et al. CJASN, 2007

Acute/Chronic Interstitial Nephritis

Sarcoidosis

• Highly steroid responsive
• 17 biopsy confirmed TIN
• 0.5 mg/kg prednisolone (30-60 mg/d)
• All improved with steroids
• All left with some level of CKD

Rajakariar et al, Kidney Int, 2006
Systemic inflammatory disease
- Lymphocytic/plasmacytic organ infiltration including the kidneys
- Women > men, 50-60 years old
- Primary or secondary (SLE, RA, Sys Scl)
- Renal involvement variable (15-67%)

Imaging and Lab testing
- Ultrasound with echogenic kidneys
- Serologies (ANA, SSA/SSB, RF, IgG)
- Bland sediment or sterile leukocyturia
- Tubular proteinuria (< 1 g/day)
- AKI with tubulopathies (Fanconi, distal RTA, NDI, CKD)

Renal histopathology
- Lymphocytic interstitial infiltrate with tubular atrophy, fibrosis
- Rare immune-complex GN

Treatment
- Hydroxychloroquine, MMF, azathioprine, steroids, methotrexate, cyclophosphamide

Idiopathic T cell disease of eyes/kidneys
- Inflammatory disease of eyes and kidneys
- Women > men, young age (median 15 yo)
- Mechanism unknown, risk factors?
- Uveitis before/during or after AIN
- Painful red eyes, +/-photophobia, fever

Imaging and Lab testing
- Ultrasound with echogenic kidneys
- Sterile leukocyturia in sediment
- Tubulopathy with proteinuria, glucosuria, and beta-2 microglobulinuria
- Eosinophilia, anemia, LFTs may be seen

Renal histopathology
- Interstitial edema with inflammatory cell infiltrate (+/- granulomas)

Treatment
- Prednisone 1 mg/kg/d for 3-6 mo with slow taper; relapse common
- MMF, methotrexate, CSA sometimes used

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Renal histopathology
- Interstitial edema with inflammatory cell infiltrate (+/- granulomas)

Treatment
- Prednisone 1 mg/kg/d for 3-6 mo with slow taper; relapse common
- MMF, methotrexate, CSA sometimes used

61 yo woman is evaluated for persistent dry cough (despite 2 different courses of oral antibiotics), malaise, fatigue, low grade fever and abdominal pain. Labs reveal WBC 11.3, Hb 10.1, Cr 1.5, and 5-10 WBCs/HPF on urine microscopy. CT scan of chest is shown. CT abdomen of the abdomen, performed for abdominal pain, is shown.

The lung mass was biopsied and read as 'lymphoplasmacytic infiltrate with reactive changes'. No evidence for cancer with numerous lymphocytes (T and B cells) and plasma cells. A kidney biopsy was obtained to make a definitive diagnosis.
What is the most likely diagnosis in this patient?
A) T cell lymphoma
B) IgG4 disease
C) Sarcoidosis
D) Castleman’s disease
E) Eosinophilic granulomatosis with polyangiitis

What is the most appropriate treatment for this patient?
A) Methotrexate and dexamethasone for lymphoma
B) Cyclophosphamide and corticosteroids
C) Corticosteroids alone
D) Mycophenolic acid and corticosteroids
E) No therapy is required at this time

Acute/Chronic Interstitial Nephritis

IgG4 Disease
- Immune-mediated disease—masses in various organs
  - Described in pancreas, also in numerous organs including kidneys
- Labs and renal imaging
  - 60% have increased serum IgG4 levels
  - Single or multiple nodular masses affecting one or both kidneys, sometimes leading to nephrectomy to exclude renal malignancy
- Histopathology
  - Difficult to differentiate from lymphoma or plasma cell dyscrasia
  - Lymphoplasmacytic infiltrate with predominance of IgG4-positive plasma cells and T lymphocytes and obliterative phlebitis
  - Interstitial fibrosis has ‘storiform’ pattern, typified by a cartwheel appearance of arranged fibroblasts and inflammatory cells
- Pathogenesis of IgG4D is poorly understood
  - Autoimmune and allergic disorder—IgG4 postulated to have a role in tolerance to allergens & in responses to certain infectious agents
- Treatment
  - Glucocorticoid responsive prior to excessive fibrosis, relapse does occur

A 65 year old woman with chronic migraine headaches presents with fatigue, malaise and poor appetite. Serum creatinine is 4.1 mg/dl. Urinalysis has SG 1.012, 1+ protein, trace LE. Urine microscopy has 2-5 WBCs/HPF. Renal ultrasound demonstrates bilateral 9 cm echogenic kidneys without hydronephrosis, calculi, or mass lesions.

Board Question

What is the likely diagnosis in this patient?

A. Acute tubular necrosis
B. Chronic interstitial nephritis
C. Chronic glomerulonephritis
D. Chronic pyelonephritis
E. Diabetic nephropathy

Chronic interstitial nephritis (CIN)

- Indolent course and in a variety of clinical settings
  - Drugs/toxins, hereditary or metabolic disorders, immune-mediated diseases, hematologic disturbances, infections, or chronic obstruction
- Laboratory findings
  - Tubular proteinuria, bland sediment (or microscopic hematuria, sterile pyuria)
  - Tubular injury:
    - Glucosuria, phosphaturia, and sodium wasting
    - Low MW proteins—lysozyme, β2-microglobulin, & retinol binding protein
- Kidney imaging
  - Ultrasonography reveals shrunken, echogenic kidneys
    - CT scan notes irregular renal contours and calcifications
- Histopathology (consistent despite varied causes)
  - Tubular cell damage, mononuclear cell inflammation, tubulointerstitial fibrosis
  - Interstitial granulomatous disease in certain forms of CIN (sarcoidosis)
  - Over time, glomerular and vascular structures are involved
  - All progressive kidney disease eventually result in chronic interstitial fibrosis

Joss et al. CJASN, 2007
Chronic interstitial nephritis

**Lithium Toxicity**

- Acute/Chronic lithium toxicity
  - AKI, CKD (CIN), FSGS, NDI
- Asymptomatic CKD with polyuria and nocturia
- **Diagnosis:**
  - Histology — tubular atrophy, interstitial fibrosis, and cystic tubules
  - CT scan — may show small renal cysts
- **Treatment:** Routine CKD care, adequate hydration setting of NDI, amiloride to reduce Li+ absorption

Chronic interstitial nephritis

**Lead Nephropathy**

- Acute/Chronic lead exposure
  - AKI, Fanconi, CKD (CIN), HTN
- Slowly progressive CKD, HTN, and gout, exacerbates other causes of CKD
- **Diagnosis:**
  - Histology — tubular atrophy, interstitial fibrosis (No proximal tubular lead inclusions as seen with acute Pb toxicity)
  - U/S or CT scan — small, shrunken hyperchoic kidneys
- **Treatment:** Routine CKD care, may benefit from Pb chelation therapy

Chronic interstitial nephritis

**Sickle Cell Nephropathy**

- Renal manifestations of Sickle Cell disease
  - Hematuria, AKI, CKD (CIN), FSGS, papillary necrosis
- Medullary/papillary microinfarction with papillary necrosis presents with asymptomatic hematuria, gross hematuria, pain, or urinary tract obstruction (unilateral/bilateral), CKD—hemosiderin/ischemia
- **Diagnosis:**
  - Urine sediment — renal tissue in sediment
  - IVP findings — partial necrosis (cavity extending out of the renal calyx), complete necrosis (ring shadow in calyx or loss of papillary surface “claw-like”), also have papillary calcification
- **Treatment:** IVFs, analgesia, relieve obstruction

Chronic interstitial nephritis

**Medullary Sponge Kidney**

- MSK results from ectasia of collecting duct
- Urinary stasis, hypocitraturia & dRTA lead to small calcium-containing nephroliths
- Asymptomatic hematuria may be presenting sign, but flank pain is common
- **Diagnosis:** Ultrasound & CT scan identify nephrocalcinosis and hyperdense papilla (CT misses 50% of MSK documented with IVP); IVP shows classic “brush-like” lesions, CT urogram similar to IVP
- **Treatment:** K+ citrate for stones/ dRTA, pain control, antibiotics for infection
Chronic interstitial nephritis/fibrosis

- **Clinical settings**
  - **Drugs:** Chronic lithium (tubular microcysts), AA/BEN
  - **Toxins/heavy metals:** Pb (gout, HTN, progressive CKD)
  - **Hereditary disorders:** Medullary sponge kidney (pain, hematuria, nephrocalcinosis, stones) with characteristic IVP/CT urogram (brush-like pyramids)
  - **Immune-mediated diseases:** Sjo Syn, Sarcoidosis, IgG4D
  - **Hematologic disturbances:** Infiltrative diseases such as lymphoma, leukemia, Sickle cell disease (hematuria, papillary necrosis)
  - **Infections:** Chronic pyelonephritis, XGP, Malacoplakia
  - **Chronic obstruction:** Any cause associated with CIN

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**BOARD MATERIAL**

- **Causes of AIN/CIN**
  - Know the classics and some new ones
  - Sarcoidosis, IgG4 disease, Sjogren, Sickle cell, TINU,
  - AAN/BEN, Lithium, Lead, MSK

- **Know the clinical presentation of CIN**
  - Common final pathway of many causes of CKD
  - Tubular proteinuria, bland sediment (or few WBCs)
  - Small, echogenic kidneys, sometimes with Ca++

- **Not likely to be on the boards**
  - Malacoplakia and XGP—pseudo-renal tumors
  - HIV-related IRIS and DILS
  - (see extra slides at the end)
**AIN/CIN**

**HIV Immune Restoration Inflammatory Syndrome**
- Immune restoration inflammatory syndrome (IRIS)
  - Prolonged, severe immunodeficiency
  - Antiretroviral naivety
  - Short delay between opportunistic therapy and HAART initiation
  - Marked viral load reduction/increased CD4 increase
- Organ involvement
  - Liver, spleen, lung, lymph node, eye, CNS, skin, intestine, bone, kidney
  - Kidney—interstitial infiltrate with granuloma; CD68 staining of cells
- Treatment
  - Steroids: 1 mg/kg/d x 1 mo with taper

**AIN/CIN**

**HIV Lymphocytosis Syndrome**
- Diffuse lymphocytosis syndrome
  - Immunologic syndrome in response to HIV antigens or other endotoxins
  - Uncommon in cART era
  - Increased CD8 lymphocytosis
  - More common in Africans
- Organ involvement
  - Parotid, liver, lung, lymph node, CNS/Peripheral nerves, spleen, muscle
  - Renal involvement ~ 10%
  - AKI/CKD, tubular proteinuria, renomegaly
  - CD8 staining of the cellular infiltrate
- Treatment
  - Steroids: 1 mg/kg/d x 1 mo with taper
  - Treat HIV and other infections

**Chronic Interstitial Nephritis**

**Renal Malacoplakia**
- Inflammatory kidney disease
  - Abnormal kidney image, AKI or pyelonephritis-like disease
- Imaging and Lab testing
  - Abnormal kidneys- malignancy?
  - Urine culture growing gram- bacteria (E coli ~70%-90% of cases)
- Renal histopathology
  - Foamy histiocytes - basophilic inclusions (Michaelis-Gutmann bodies)
- Immunosuppression (major risk)
  - Autoimmune disease, kidney transplant, diabetes, malignancy
  - Alcohol abuse and associated malnourished state
- Treatment
  - Antibiotics (TMP/SFX and ciprofloxacin)
  - Bethanechol and ascorbic acid
  - Bilateral disease & transplant patients fare worse
  - Early diagnosis and antibiotics are imperative

**Renal Malacoplakia**
- Michaelis-Gutmann bodies
**Inflammatory kidney disease**
- Abnormal kidney image, flank mass/pain, fever/sepsis, and/or AKI

**Imaging and Lab testing**
- Abnormal kidneys—mass, hydronephrosis, staghorn calculi in ~80%, focal or diffuse kidney involvement, extrarenal lesions
- Urine culture growing gram- bacteria
  - *E coli*, *Proteus*, *Klebsiella*, *Providencia*, rarely Staph sp

**Renal histopathology**
- Lipid laden, foamy macrophages (xanthoma cells); inflammatory cells

**Risk groups**
- Recurrent UTIs, staghorn stone formers

**Treatment**
- Antibiotics (TMP/SFX and ciprofloxacin)
- Nephrectomy (partial nephrectomy)
- Extension to other organs, cutaneous fistula, need surgical excision

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**Chronic Interstitial Nephritis**
* Xanthogranulomatous Pyelonephritis


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**Xanthogranulomatous Pyelonephritis**