Nephritis

Joe Ghata
ACP, 10/5/19
"Never worry about numbers. Help one person at a time, and always start with the person nearest you."
~ Mother Teresa
Case 1

82 year old male with Alzheimer's Disease and with mitral valve endocarditis secondary to strep viridians is discharged home on intravenous penicillin via an upper extremity central line. Three weeks later he presents with the central line site is clear. On exam, he has a pruritic maculopapular rash on his legs and trunk. Vital signs are temperature 39.7°C, pulse of 90 beats/min, respirations 18/min, and blood pressure of 140/85 mm Hg. Labs reveal a WBC of 13,500/microliter, with 75% PMN, 8% lymphocytes, 4% monocytes and 13% eosinophils. Previous BUN/creatinine was 13/0.9, but now is 60/2.3. Electrolytes and complement levels are otherwise normal. Repeat blood and urine cultures are pending.

What is the most likely diagnosis?

A. Acute interstitial nephritis
B. Immunoglobulin A Vasculitis (HSP nephritis)
C. Pyelonephritis
D. Acute tubular necrosis
E. Post-infectious Glomerulonephritis
Objectives

• History of Interstitial Nephritis
• Anatomy and Physiology of Kidney
• Acute Renal Pathophysiology Primer
• Types of Hypersensitivity Reactions
• Acute Interstitial Nephritis Diagnostics and Etiologies
• AIN Clinical Course and Treatment
• Take-Home Message
History of Nephritis
Milestones

• Before the 1800s, the kidney was considered a tubulosecretory organ.
• 1827 - report of dropsical albuminuric medical cases by Richard Bright.
• 1858 - Rudolph Virchow report of nephritis affecting tubules, interstitium, and vasculature.
• 1862 - First Case Report by Micheal Anton Biermer.
• 1869 - Edwin Klebs added glomerular nephritis.
THE JOURNAL
OF
EXPERIMENTAL MEDICINE

ACUTE INTERSTITIAL NEPHRITIS.

BY W. T. COUNCILMAN, M. D.

(From the Sears Pathological Laboratory of Harvard University.)

Plates XXXVII and XXXVIII.

Definition.—An acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependent on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal.

This condition was first described by Biermer (1). He found the kidneys of a child four and a half years old, who died of scarlet fever, greatly swollen, the surface pale, and on microscopical examination showing intense infiltration of the connective tissue with lymphoid cells. He considers the formation of lymphoid tissue here analogous to that found in typhoid fever. The cellular infiltration is more marked in the pyramids than in the cortex. E. Wagner (2) describes a similar case, in which,
Anatomy and Physiology
Acute Renal Failure
1. Pre-renal azotemia
   Hypovolemia
   Cardiac failure
   Hepatorenal syndrome

2. Renal artery
   Renal artery occlusion
   Large- or medium-vessel vasculitis

3. Small-vessel disease
   Thrombotic microangiopathy
   Renal atheroembolism
   Small-vessel vasculitis

4. Glomerular disease
   Anti-GBM disease
   Lupus nephritis
   Postinfectious glomerulonephritis
   Infective endocarditis
   Membranoproliferative glomerulonephritis
   Cryoglobulinemia
   IgA nephropathy/Henoch-Schönlein purpura

5. Acute tubular necrosis
   Ischemia
   Nephrotoxins
   Rhabdomyolysis
   Radiographic agents

6. Acute interstitial nephritis
   Drugs
   Infection
   Systemic disease

7. Intratubular obstruction
   Cast nephropathy
   Drugs
   Crystalluria

8. Post-renal obstruction
   Bladder outlet obstruction
   Tumors
   Renal calculi
   Papillary necrosis
   Retroperitoneal fibrosis

9. Renal vein
   Renal vein thrombosis
Ischemia/reperfusion → Toxicity → Damage → Necrosis → Apoptosis

Normal epithelium

Potential urinary biomarkers for early diagnosis of AKI:

- NAG
- β₂M
- α₁M
- RBP
- Cystatin C
- KIM-1
- Clusterin
- Microalbuminuria

NGAL, CYR-61, IL-18, OPN, FABP, NHE3, Fetuin A

Delayed biomarkers for kidney injury:

- ↑ Serum creatinine
- ↑ Blood urea nitrogen

↓ GFR
GFR Criteria

- Increased serum creatinine ×1.5 or GFR decrease >25%
- Increased serum creatinine ×2 or GFR decrease >50%
- Increased serum creatinine ×3 or GFR decrease >75% or serum creatinine >4mg/dl or acute rise >0.5mg/dl

Urine Output Criteria

- UO <0.5ml/kg/h × 6 hrs
- UO <0.3ml/kg/h × 24 hrs or anuria × 12 hrs

Risk
Injury
Failure
Loss
ESKD

High Sensitivity
High Specificity

Persistent ARF = complete loss of kidney function >4 weeks
End stage kidney disease > 3 months
Complications:

- Normal
- Increased risk
- Damage
- ↓ GFR
- Kidney failure
- Kidney death
Hypersensitivity Reactions
<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgE-Mediated Hypersensitivity</strong></td>
<td><strong>IgG-Mediated Cytotoxic Hypersensitivity</strong></td>
<td><strong>Immune Complex-Mediated Hypersensitivity</strong></td>
<td><strong>Cell-Mediated Hypersensitivity</strong></td>
</tr>
<tr>
<td>Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators</td>
<td>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC</td>
<td>Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils</td>
<td>Sensitized T&lt;sub&gt;H&lt;/sub&gt;1 cells release cytokines that activate macrophages or T&lt;sub&gt;C&lt;/sub&gt; cells which mediate direct cellular damage</td>
</tr>
<tr>
<td>Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema</td>
<td>Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia</td>
<td>Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus</td>
<td>Typical manifestations include contact dermatitis, tubercular lesions and graft rejection</td>
</tr>
</tbody>
</table>
(A) Naive CD4+ T cell activation leads to the differentiation into Th1, Th2, and Th17 cells.

Th1 cells: IFN-γ secretion; host defense against intracellular microbes; inflammation

Th2 cells: IL-4, IL-5, IL-13 secretion; host defense against helminths; allergic reactions

Th17 cells: IL-17 secretion; host defense against some bacteria and fungi; inflammatory disorders

(B) Property | Th1 | Th2 | Th17
--- | --- | --- | ---
Principal cytokines produced | IFN-γ | IL-4, IL-5, IL-13 | IL-17, IL-22
Antibody isotypes stimulated | Complement and Fc receptor-binding IgG subclasses such as IgG2a (mouse) | IgE; IgG1 (mouse), IgG4 (humans) | ?
Macrophage activation | Classical (microbial killing) | Alternative (tissue repair) | ?
Dominant leukocytes recruited | Monocytes | Eosinophils | Neutrophils, monocytes
Activation of macrophages

Responses of activated macrophages

Killing of phagocytosed microbes

Increased expression of MHC molecules and costimulators (B7 molecules)

Secretion of cytokines (TNF, IL-1, chemokines, IL-12)

CD40
CD40L
Macrophage with ingested microbes

IFN-γ

CD4+ effector T cell (TH1 cell)

IFN-γ receptor

ROS, NO
A. Phagocytes with ingested microbes; microbial antigens in vesicles

- CD4+ effector T cells (TH1 cells)

  → Cytokine secretion

  → Macrophage activation; killing of ingested microbes

  → Inflammation

B. Infected cell with microbes in cytoplasm

- CD8+ T cells (CTLs)

  → Killing of infected cell
CTL

Infected "target" cell

Antigen recognition and conjugate formation

CTL activation

CTL granule exocytosis

Apoptosis of target cell

Granzyme, Perforin, Serglycine

Granzymes enter cell via receptor-mediated endocytosis, and enter cytoplasm via perforin-independent mechanisms → activation of apoptotic pathways.
Acute Interstitial Nephritis
Acute Interstitial Nephritis

• A common cause of intrinsic AKI
  • Now, the second leading after ATN

• AIN may be more common in AKI since biopsies often not performed
    • AIN was seen in 19% of biopsies in a study in USA (Haas et al. American journal of kidney diseases 2000)
    • Nearly 8-fold increase in AIN in a study in Spain (Goicoechea et al. Nephrol Dial Transplant 2013)
  • 1% of “healthy” people biopsied for isolated proteinuria/hematuria
  • 1-15% of all biopsies in patients with renal disease
<table>
<thead>
<tr>
<th></th>
<th>Acute Tubular Necrosis</th>
<th>Acute Interstitial Nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset following injury</td>
<td>Hours to days</td>
<td>Days to weeks</td>
</tr>
<tr>
<td>Urine volume</td>
<td>Oliguria (&lt; 500 mL/d)</td>
<td>Polyuria (&gt; 2,000 mL/d)</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Hemodynamic instability</td>
<td>Rash (25 – 40%), fever (35 – 70%), back pain (25 – 40%), arthralgia (25 – 40%)</td>
</tr>
<tr>
<td>Histology</td>
<td>Tubular epithelial cell injury</td>
<td>Interstitial cellular infiltrates, edema, tubulitis</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Absent</td>
<td>Present (35 – 60%)</td>
</tr>
<tr>
<td>Tubular dysfunction†</td>
<td>Rare</td>
<td>Very common</td>
</tr>
<tr>
<td>$\text{FE}_{Na}$</td>
<td>&gt; 1%</td>
<td>&gt; 1%</td>
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</table>
Each stage may require unique therapies to address operative pathways.
Clinical Presentation of AIN

<table>
<thead>
<tr>
<th>Features</th>
<th>%</th>
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<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>
<tr>
<td>Microhematuria</td>
<td>67%</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>5%</td>
</tr>
<tr>
<td>Leukocyturia</td>
<td>82%</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>

Triad: 10%
Diagnosis

• Renal biopsy remains the definitive diagnostic modality
  • Hallmark of AIN:
    • Inflammatory interstitial infiltrate of monocytes and lymphocytes (fewer eosinophils, plasma cells, and neutrophils)
    • Interstitial edema
    • Renal tubule separation
    • Tubulitis
    • Absence of glomerular or vascular pathology
  • Fibrotic changes may be seen as early as within 7-10 days
  • Granuloma patterns can occur and commonly are drug-related

Interstitial Inflammation and Edema
Pathological pattern of CIN

Interstitial Fibrosis, Tubular Atrophy, and “Benign” Hyaline casts

Tamm-Horsfall (Uromodulin)
Types of TIN

• Primary TIN – limited to the tubulointerstitium, associated with drugs. Glomeruli and vessels are uninvolved.
• Secondary TIN – associated with a primary glomerular, vascular or systemic disease.
• Reactive TIN – inflammation from effects of systemic infection, where kidneys are usually sterile
• Idiopathic TIN – unknown pathology
Etiologies of AIN

• Drugs (Allergic interstitial nephritis) (70-75%)
  • Antibiotics: 30-50%
  • Mean delay between drug start date and AKI is 10 days
  • Latent period can be as short as 1 day with some antibiotics

• Systemic disease (10-20%)
  • Autoimmune diseases (Sarcoidosis, SLE, Sjögren's, ANCA)
  • Neoplastic (leukemias, lymphomas)
  • Acute allograft rejection

• Infections (bacterial, viral, parasitic) (5-10%)

• Idiopathic (5-10%)
  • Hypocomplementemic AIN with TBM Antibodies
  • IG4 related TINU
Drugs Related Allergic Interstitial Nephritis

- **Antibiotics**: PCN, cephalosporins, ciprofloxacin, rifampin, sulfa, vanco, erythromycin, Sulfamethoxazole/Trimethoprim (bactrim), acyclovir, ethambutol (EMB)
- **Diuretics**: thiazides, furosemide, bumetanide, triamterene
- **NSAIDS** (including selective COX-2 inhibitor): pure interstitial nephritis (ISN) ± papillary necrosis/ minimal change nephropathy (MCN) + ISN (85%)
- **PPI** (omeprazole and lansoprazole)
- **H2 blockers** (cimetidine, ranitidine-rare)
- **Allopurinol**
- **Indinavir**
- **5-aminosalicylates (5-ASA)** (i.e. mesalamine)
- **Others**: phenobarbital, phenytoin, nitrofurantoin, IFN, IL-2, Angiotensin converting enzyme inhibitor (ACEI: i.e. captopril), checkpoint inhibitors
Case 2

• A 24 yo male with a hx for aplastic anemia s/p umbilical cord stem cell transplant c/b CMV viremia and EBV related post-stem cell PTLD of his lungs and intestinal tract treated with Rituximab; ESRD from TTP/HUS-induced chronic TMA on hemodialysis, who is postop day #4 s/p living unrelated kidney transplant.

• His U.O.P decreased from 750 cc/hr post-op to 20 cc/hr. His Cr increased to 5.5 after initially going down from 6.64 to 3.73 post-op.

• He was last dialyzed the day prior to transplantation without complication.
Case 2

- **Medications**: Valganciclovir (valcyte), tacrolimus, MMF, prednisone, labetalol, Amlodipine, Minoxidil, Sulfamethoxazole/Trimethoprim (bactrim)

- **PE**: Temp 99.4 BP 127/71 HR 118 RR 16, INS/OUTS: 2700/480, JVP ~ 12 cm, mild tenderness to palpation of LLQ at surgical site. trace lower extremity edema. foley draining dark yellow urine

- **Lab**: Urinalysis: 1.015/5.0, 2+ protein, 61 RBCs, 6 WBCs, Na 131, HCO3 18, Cr 5.5, BUN 84, WBC 10.5, Hb 10, Hct 29.6

- **Renal Biopsy**: Kidney allograft biopsy, 4 days post-transplantation:
  - Acute Interstitial Inflammation; The changes are most likely an expression of a acute interstitial nephritis. However, acute rejection could have resulted in similar changes
AIN: Transplant rejection pattern
Case 2 - Bactrim and DRAIN

• TMP-SMX is the standard PJP prophylaxis in transplantation.
  • Josephson, et al. AJKD, 34(3): 540-548, September 1999
    • 6 patients with delayed graft function (DGF) and drug-induced interstitial nephritis
    • 5/6 occurred within 4 weeks of transplantation
    • 11/109 (10.1%) biopsies performed for early allograft dysfunction
    • early allograft dysfunction defined as < 1 month
    • TMP-SMX stopped and creatinine immediately improved
Drug-induced Hypersensitivity Reaction Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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| Type IVa       | T helper 1 cell  
Interferon-γ/Interleukin-12  
- Monocyte/macrophage stimulation  
- Synthesis of complement-fixing antibody and complement-mediated injury  
- Co-stimulation of pro-inflammatory responses (tumor necrosis factor, interleukin-12)  
- Co-stimulation of CD8 T-cell responses |
| Type IVb       | T helper 2 cell  
Interleukin-4, interleukin-5, interleukin-13  
- B-cell production of IgE and IgG4  
- Macrophage deactivation  
- Mast cell and eosinophil responses |
| Type IVc       | Cytotoxic T cells  
- Injury via perforin/granzyme and Fas ligand-dependent processes |
| Type IVd       | T cell (interleukin-8 and granulocyte-monocyte-colony stimulating factor)  
- Neutrophil-mediated inflammation/'sterile polymorphonuclear-rich inflammation' |
Clinical Course of AIN

- Most resolve with removal of offending agent/ treatment of underlying infection
- Up to 1/3 may need dialysis
- Likelihood of recovery inversely proportional to degree of renal failure
  - Scattered infiltrates associated with better outcome (Buysen et.al. NDT 1990; Laberke et.al. Clin Nephrol 1980)
- 50% of idiopathic remain with some renal dysfunction
Treatment of AIN

• NSAID-induced AIN: withdraw of the offending drug
  • Addition of steroids does not change the clinical course (Porile et.al. J Clin Pharmacol 1990)

• Steroids: mainstay of treatment in idiopathic AIN, TINU and AIN associated with systemic diseases (Rossert KI 2001; Neilson KI 1989; Finkelberg et.al. NEJM 2006; Yoneda et.al. AJKD 2007)

• Cyclophosphamide; Cyclosporine: steroid-resistant idiopathic AIN (Zuliani et.al. Clin Nephrol 2005)

• Mycophenolate Mofetil (MMF): steroid dependent, resistant AIN; or unable to tolerate steroid therapy (Preddie et.al. Clin J Am Soc Nephrol 2006)

• Plasmapheresis or cytotoxics: if strong anti-TBM Ab
Role of Steroids

• There are no prospective randomized controlled trials to date to assess the efficacy of steroids in treatment.

  
  • One series with Methicillin-induced AIN: 14 patients with average peak Cr of 8 mg/dL. 8 patients received glucocorticoids. These patients recovered more quickly (9 versus 54 days) and had a lower final Cr level (1.4 versus 1.9 mg/dL) than the six who received no therapy.
  
  • One series with biopsy-proven AIN: total of 27 patients (15 drug induced; 9 due to infection; 3 idiopathic)
    
    • The 10 patients who did not improve after stopping the drug or treatment of the infection were given glucocorticoids within 5 to 20 days of biopsy. 6 patients had normalized Cr within ~one month, and the remaining 4 had partial improvement in kidney function.
Role of Steroids


• Multi-center study with 61 patients: 52 patients (85%) received steroids vs 9 patients (15%) did not (Gonzalez, et al. Kidney International, 73:940-946, 2008)
  • Lower % of dialysis by 18 months (3.8 % vs. 44%)
  • Lower Cr level (2.1 vs 3.7 mg/dL)
  • Those received steroids < 7 days of stopping offending drug were more likely to recover kidney function (Odds ratio 6.6,95% CI 1.3-33.6)

• Single center study with 60 biopsy-proven AIN patients: 42 follow-up data, 25 (60%) received steroid treatment and 17 (40%) did not (Clarkson, et al. Nephrol Dial Transplant, 19:2778-2783, 2004)
  • no difference in Cr observed at 1, 6 and 12 months

• Another series with 95 biopsy-proven AIN: 83 patients received steroids and 12 did not (Muriithi et al Am J Kidney Dis 2014)
  • At six months, there was no difference in the probability of recovery of renal function between the group given steroids and the group not given steroids
KDOQI Guidelines

• Treat patients who do not have significant improvement in the Cr within 3-7 days after discontinuation of the offending agent
  • a renal biopsy is preferred
    • to confirm AIN
    • to exclude other possible diseases
    • Assess the present of interstitial nephritis with significant chronic damage (interstitial fibrosis, tubular atrophy, and minimal or no acute inflammation), in which case immunosuppressive therapy might not be indicated
• An empiric trial for patients with a strongly suggestive history of DRAIN when kidney biopsy is not feasible
• The optimal dose and duration of therapy are unclear
  • Administer prednisone at a dose of 1 mg/kg per day (max 40 to 60 mg) for 1-2 weeks with gradual taper for a total therapy duration of 2-3 months.
  • In more severe AKI, use IV methylprednisolone (0.5 to 1 g/day for three days)
  • The duration of steroids varies widely among the many (cohort) studies in the literature, from days to 12 weeks (Rossert J. KI 2001; Galpin et al. Am J Med 1978; Handa SP CMAJ 1986; Buysen et al NDT 1990)
Take-home Message

• ATN and AIN constitute 85% causes of intrinsic AKI
  • The remaining 15% have a high component of accompanying ATN and AIN

• The “triad” of AIN: fever, rash and eosinophilia
  • Only seen in ~ 10% of patients with AIN
  • Absence of “triad” does not r/o AIN

• Drugs are a common cause of AIN
  • Most of the Drug-Related AIN improve spontaneously after stopping the offending agent.
  • Clinical suspicion for drug-induced nephrotoxicity should be high
  • Delayed intervention results in poor renal outcomes

• Steroid remains as the mainstay treatment option for AIN
  • The optimal dose and duration are currently unclear