Acute Interstitial Nephritis

Background
1. Definition
   - Acute renal insufficiency caused by immune-related damage to the renal tubules and interstitium
   - Damage is caused by a hypersensitivity reaction; not direct toxicity

2. General info
   - Medications are the most common cause (40-60%\(^{1,3}\))
     - Reaction is unrelated to dosage
   - Medications
     - Antibiotics
       - Cephalosporins, penicillins, sulfa, rifampin
     - NSAIDs (all)
     - Diuretics
     - Allopurinol
     - All medications are candidates
   - Infections
     - Primary renal (pyelonephritis) or systemic (legionella, HIV)
   - Immune/neoplastic disorders
     - SLE, sarcoidosis
   - Toxins
     - Lead, other heavy metals
     - Cocaine

Pathophysiology
1. Pathology of disease
   - Interstitium is infiltrated with inflammatory cells
     - Glomeruli and vessels are spared
   - Exact cause is poorly understood
   - Immune etiology is suggested by:
     - Delayed onset of the reaction
     - Recurrence of symptoms following re-exposure
     - Absence of a dose-related effect
     - Frequent presence of IgE containing basophils and plasma cells (type 1 mediated hypersensitivity) in the interstitium
     - Presence of mononuclear infiltrate with positive skin tests to antigens (delayed type IV hypersensitivity reaction)
   - One theory is that drugs act as haptons
     - After being secreted by tubules they bind to a receptor on interstitial cells and stimulate immune response\(^2\)

2. Incidence, prevalence
   - 5-15% of all hospitalizations for acute renal failure\(^{1,4}\)

3. Risk factors
   - Age >60
   - Exposure to known medication
   - Infection
   - Immune/neoplastic disorder
4. Morbidity / mortality
   - Only rarely associated with chronic renal failure

**Diagnostics**

1. History
   - Inquire about new medications started about 2 weeks prior to the development of symptoms
   - Non-specific symptoms of renal failure (anorexia, fatigue, vomiting)
   - Classic triad of fever, rash, and arthralgias occurs about 5% of the time
   - Rarely flank pain, hematuria
   - Other findings associated with underlying disease process (HIV)

2. Physical exam
   - Similar to other causes of renal insufficiency (oliguria, periorbital edema)
   - May have non-specific rash, tenderness with joint manipulation

3. Diagnostic testing
   - Laboratory evaluation
     - Elevated BUN/creatinine
     - Fractional excretion of sodium (FeNa) usually >1%
     - Urine eosinophils of questionable utility (one small study revealed a PPV = 38%, NPV = 74% 6)
   - Diagnostic imaging
     - Ultrasonography is non-diagnostic
     - Normal to enlarged kidney size with increased cortical echogenicity
     - Some small studies show Gallium 67 scanning helpful in distinguishing acute interstitial nephritis from acute tubular necrosis
   - Other studies
     - If necessary, definitive diagnosis is made by renal biopsy

4. Diagnostic criteria
   - Renal biopsy findings of plasma cell and mononuclear infiltrates in peritubular areas of the interstitium

**Differential Diagnosis**

1. Key DDx
   - Acute tubular necrosis (ATN)
   - Glomerulonephritis
     - Post-streptococcal
     - IgA nephropathy
     - Alport syndrome
     - Lupus nephritis
     - Membranoproliferative GN
   - Other causes of acute renal failure (ARF)

2. Extensive DDx
   - ARF: Prerenal cause
     - Sepsis, CHF, hemorrhage, over-diuresis
   - ARF: Intrinsic renal causes
     - Tubular disease
       - Acute tubular necrosis (ATN)
       - Aminoglycoside toxicity
- Contrast-induced nephropathy
- Glomerular disease
  - Post-streptococcal
  - IgA nephropathy
  - Alport syndrome
  - Lupus nephritis
  - Membranoproliferative GN
- Vascular disease
  - Microvascular
    - Atheroembolic disease
    - Thrombotic thrombocytopenic purpura (TTP)
    - HELLP syndrome
  - Macrovascular
    - Abdominal aortic aneurysm
    - Renal artery stenosis
- Interstitial disease
  - ARF: Post-renal causes
    - Benign prostatic hypertrophy (BPH)
    - Neurogenic bladder
    - Urethral stricture
    - Nephrolithiasis

**Therapeutics**

1. **Acute treatment**
   - Withdrawal of offending agent
   - Hospitalization and supportive care
   - Close monitoring for improvement of renal function

2. **Further management (24 hrs)**
   - If not showing improvement, consider nephrology consultation
   - Consider renal biopsy (preferred) if no contraindications exist
     - Gallium-67 scanning may be useful if unable to perform biopsy
   - Small case reports suggest steroids may be beneficial\(^{1,4,5}\)
     - Prednisone 1 mg/kg daily by mouth, tapering over 3-4 weeks
     - May also use equivalent IV dose
   - Consider other immunomodulators (cyclophosphamide) in patients who do not respond to a 2-3 week course of steroids

3. **Long-term care**
   - Follow renal function until it returns to baseline
   - If medication is the suspected cause, it should be avoided and clearly identified in patient record as the cause of an adverse reaction

**Follow-Up**

1. **Return to office**
   - 2-4 days after discharge from hospital\(^8\)
   - Reassess renal function and reconcile outpatient medications

2. **Refer to specialist**
   - May require follow-up with nephrology
Prognosis
1. If offending medication is withdrawn early, most patients regain normal renal function in a few weeks

Prevention
1. Careful and deliberate use of medications known to cause interstitial nephritis

Patient Education
1. AAFP - Kidney Failure
   ○ http://www.aafp.org/afp/20030615/2539ph.html

References

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