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 haptens
     - 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[7]
    - 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

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