Wegener's Granulomatosis

Background
1. Form of systemic vasculitis with "classic" and "limited" forms
2. Classic Wegener's involves a triad of upper respiratory disease, lower respiratory disease and glomerulonephritis
   - Upper respiratory disease:
     - Sinusitis, nasal obstruction, otitis media, mastoiditis
   - Lower respiratory disease:
     - Cough, dyspnea, hemoptysis
   - Glomerulonephritis (GN):
     - Asymptomatic, acute renal failure
3. Limited form - isolated upper or lower respiratory disease
   - Occurs in approx 25% of cases
   - Up to 80% will eventually develop GN

Pathophysiology
1. Type III immune complex mediated hypersensitivity
   - Results in necrotizing vasculitis of small and medium arteries
2. Prevalence - 3 per 100,000
3. Risk factors: males, >50% Caucasian, age 50-60 years
4. Morbidity:
   - Musculoskeletal:
     - Myalgias
     - Arthralgias
     - Arthritis
   - Venous thromboembolism common (7 per 100 person-years)
   - Respiratory:
     - Alveolar hemorrhage
   - Dermatologic:
     - Vesicular and hemorrhagic lesions
     - Palpable purpura
   - Renal:
     - Renal failure
     - Rapidly progressive glomerulonephritis
   - Cardiac:
     - Dilated cardiomyopathy
     - Pericarditis
     - Conduction abnormalities
   - Neurologic:
     - Mononeuritis multiplex
     - CNS lesions
     - Ocular abnormalities (scleritis, corneal ulcer, uveitis, optic neuropathy)
   - GI, GU and reproductive manifestations less common
5. Mortality:
   - If untreated:
     - 90% mortality rate at 2 years
   - Treated with cyclophosphamide:
     - Mortality rate 20-28% at 5 years and 35% at 10 years
Other therapies may have better prognosis
Chronic renal failure most common cause of death

Diagnostics

1. History
   - Nonspecific complaints:
     - Night sweats, anorexia, arthralgias, wt loss common, fever (90%)
   - Pulmonary involvement (100%)
     - May be asymptomatic in 1/3 in limited form
   - Upper or lower airway dz
     - Hemoptysis, sinusitis, chronic nasal discharge, dyspnea
   - Acute or chronic renal failure

2. Physical exam
   - Skin:
     - Vasculitic lesions, rash, palpable purpura, subcutaneous nodules
   - HEENT:
     - Mucosal ulcerations, exophthalmos, saddle nose deformity, hearing loss, otitis, neuritis, hyperplastic gingivitis
   - Lung:
     - Pneumonitis and pleural effusion
   - Tumor-like masses in lung, breast and kidney

3. Diagnostic testing
   - Laboratory evaluation
     - Anti-neutrophil cytoplasmic antibodies (ANCA): (SOR:B)
       - Indirect immunofluorescence: c-ANCA or p-ANCA patterns
       - Enzyme-linked immunosorbent assay (ELISA) of PR3-ANCA and MPO-ANCA antibodies
       - Up to 90% ANCA positive with active generalized disease
         - Only 60-70% sensitive with limited form
     - Microscopic hematuria
     - Tissue biopsy at site of active disease used to confirm diagnosis
     - Skin lesions preferred due to less invasive procedure

4. Diagnostic imaging
   - Chest x-ray
     - May show cavitory nodules, alveolar or pleural opacities
   - Chest CT
     - May show wedge shaped densities, narrowing of bronchial lumen, enlarged peripheral pulmonary arteries, hemorrhage or infiltrates
   - Angiography
     - May show aneurysmal dilation
   - Echocardiography
     - May show systolic dysfunction or pericardial effusion

5. Diagnostic "Criteria"
   - Nasal or oral inflammation
     - Painful or painless ulcers or purulent or bloody nasal discharge
   - Abnormal CXR showing nodules, fixed infiltrate or cavities
   - Urinary sediment
     - Microscopic hematuria >5 RBCs/hpf with or without RBC casts
   - Granulomatous inflammation on biopsy of artery or perivascular area
6. Other testing:
   a. CBC
      - Leukocytosis, thrombocytosis, normochromic normocytic anemia
   b. ESR (marked elevation)
   c. Serum creatinine (marked elevation)
   d. UA (red cells, red cell casts, proteinuria)
   e. RF (negative)
   f. ANA (negative)
   g. Hepatitis serology (negative)

7. Treatment may be predicated on positive ANCA results
   a. Seek histopathologic confirmation before beginning long term treatment

**Differential Diagnosis**

1. Key DDx
   a. Polyarteritis Nodosa (PAN)
      - Auto-antibodies rarely present
      - Non-granulomatous
   b. Anti-GBM antibody (Goodpasture's) dz
      - Positive anti-GBM antibody
      - Negative ANCA serology
      - Limited to pulmonary and renal involvement
   c. Churg-Strauss Syndrome
      - Typically c-ANCA negative
   d. Systemic lupus erythematosus
      - Negative ANCA serology

2. Extensive DDx
   a. Sjögren's syndrome
      - ANCA negative
      - Lacrimal and salivary gland involvement
   b. Microscopic polyangiitis
      - Typically c-ANCA negative
   c. Renal limited vasculitis
      - Negative ANCA serology
      - No systemic manifestations
   d. Drug-induced ANCA associated vasculitis
      - Propylthiouracil, hydralazine, minocycline
   e. Inflammatory myopathies
      - Primarily muscle and skin involvement
      - No renal and pulmonary Sx
   f. Rhinitis
      - Limited to nose
      - No renal and pulmonary Sx

**Therapeutics**

1. Initial therapy
   a. High-dose steroids (PO or pulse IV) and cyclophosphamide (PO or pulse IV) until remission induced
      - Remission may take 3-6 months
Methylprednisolone or prednisone: (SOR:B)
- Pulse therapy - all patients with necrotizing/crescentic GN or severe respiratory dz
  - 7-15 mg/kg (max 500-1000 mg/day) for 3 days
- PO therapy - on day one or after pulse therapy (if pulse therapy indicated)
  - 1 mg/kg per day for 2-4 weeks (max 80 mg/d)
  - Tapered to 20 mg per day by the end of 8-10 weeks
  - Maintain 20 mg/d x2 weeks
  - Then reduce dose by 2.5 mg/week until taking 10 mg/d
  - Then reduce dose by 1 mg/week until off

Cyclophosphamide (CYC) for 3-6 months to induce remission: (SOR:B)
- PO therapy (1.5-2 mg/kg per day)
- Pulse IV (0.5-1 g/sq.meter body surface area every few weeks)
- PO therapy has led to fewer relapses
- Drink eight 8 oz glasses of water per day – avoids cystitis
- CBC every 2 weeks and UA monthly
- Pneumocystis carinii prophylaxis - always

Methotrexate may be substituted for cyclophosphamide in mild disease if serum creatinine <2 mg/dL (SOR:B)
- PO therapy weekly:
  - Start with 0.3 mg/kg, max 15 mg
  - Increase by 2.5 mg each week, to max 20-25 mg/week
- Combine with steroids as with CYC

2. Once proteinurinai or hematuria develop - rapid progression to renal failure
3. Maintenance therapy (SOR:B)
- Cytotoxic therapy with methotrexate OR azathioprine preferred over cyclophosphamide
  - Usually continued 1-2 years after remission
- Methotrexate:
  - PO weekly 0.3 mg/kg, max 15 mg
  - Increase by 2.5 mg each week to max 20-25 mg/week
- Azathioprine:
  - 2 mg/kg/day
  - Decrease to 1.5 mg/kg per day at 1 year

Glucocorticoids
- May be slowly tapered after 1 month or maintained on low dose/alternate day dosing for duration of therapy

Trimethoprim/Sulfamethoxazole (SOR:C)
- Mechanism of action unclear
- Proven as maintenance therapy in RCTs up to 2 years out
- Use only in mild cases; weigh benefits and risk

Follow-Up
1. Serial ANCA titers may predict relapse - measured every 2 months
   - Predictive value of increased ANCA titer for relapse
     - 57% for cytoplasmic/classic ANCA
     - 71% for PR3-ANCA
     - 100% for MPO-ANCA
2. Referral to rheumatologist, pulmonologist or nephrologist – based on clinical/objective evaluation
3. Continue monitoring CBC and UA after CYC discontinued

References
3. Finkielman, JD. ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med 01-JUL-2007; 120(7): 643.e9-14

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