Vasculitis: What The Primary Care Physician Needs To Know

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Disclosures

- **No financial disclosures for any of the presenters**
- **Rituximab and mepolizumab are the only FDA-approved medications for ANCA-associated vasculitis. Application of all other therapies constitutes off-label usage.**

Objectives

- Review classification of vasculitis
- Describe organ-specific manifestations
- Discuss common clinical presentations
- Depict a logical approach to diagnosis
- Outline approach to management
- Highlight important concurrent, comorbid, and follow-up considerations

Definition & Classification of Vasculitis

- Inflammation of the walls of blood vessels

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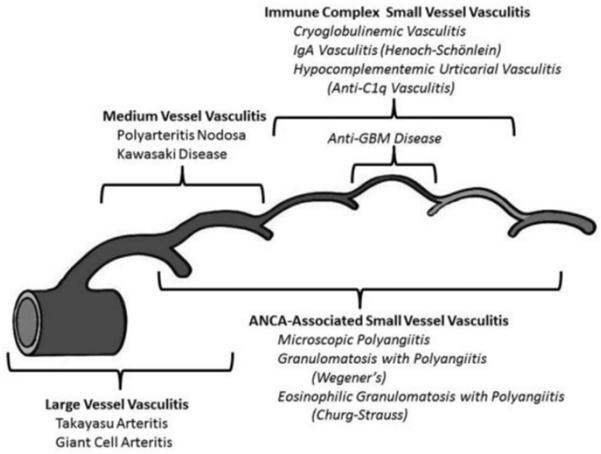

Jennette JC. Arthritis Rheum 2013; 65: 1-11

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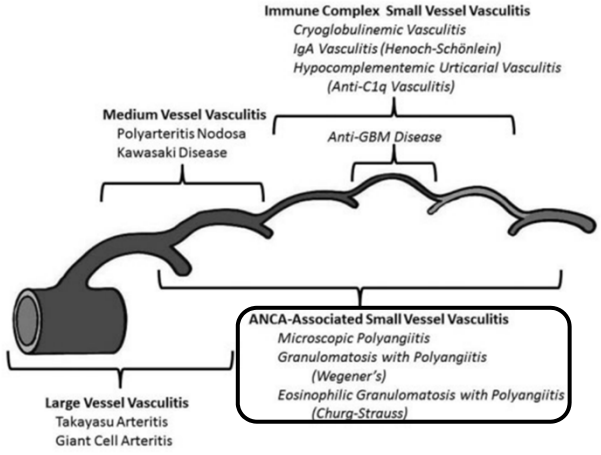

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ANCA-Associated Vasculitis (AAV)

- **Heterogeneous group of diseases**
  - **Microscopic polyangiitis (MPA)**
  - **Granulomatosis with polyangiitis (GPA)**
  - **Eosinophilic granulomatosis with polyangiitis (EGPA)**
  - **Renal-limited vasculitis (RLV)**

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- **Morbidity, mortality and organ damage are attributable to the underlying disease and to complications of immunosuppressive therapy**
- **Multi-organ involvement, necessitating multidisciplinary care**

AAV: Pathophysiology

- Role of infection
  - Frequently preceded by URI symptoms
  - Staph aureus colonization associated with risk of relapse
  - CpG stimulates ANCA production in vitro

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Hurtado PR. BMC Immunology 2008;9:34.
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- Role of ANCA
  - ANCA can induce neutrophil activation and degranulation
  - In mouse models, anti-MPO and anti-PR3 have produced varying degrees of inflammation, glomerulonephritis, and pulmonary hemorrhage
  - Relapse uncommon with undetectable B cells or ANCA
- Role of complement, C5a

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AAV: Defining Features

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  - **Myeloperoxidase (MPO-ANCA)**
  - **Proteinase 3 (PR3-ANCA)**

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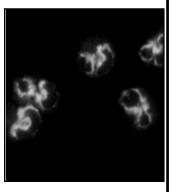

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Images courtesy Ulrich Specks, MD
Hoffman GS. Arthritis Rheum 1999;41:1521-37.

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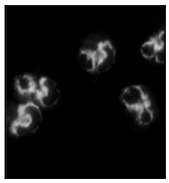
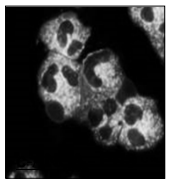
    - **Cytoplasmic (c-ANCA) staining pattern**





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AAV: Defining Features

- **Necrotizing inflammation of small blood vessels, most characteristically capillaritis**
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  - **Lungs and trachea**
  - **Kidneys**
  - **Eyes and orbit**
  - **Skin**
  - **Nervous system**

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  - **Peripheral eosinophilia**
  - **Cardiomyopathy**

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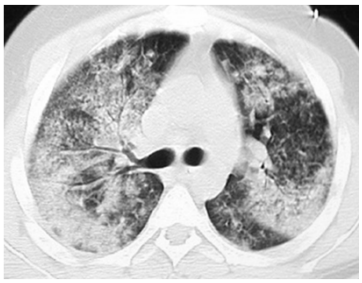
May have acute or subacute presentation, inpatient or outpatient setting

ENT and Pulmonary Manifestations of AAV

Alveolar Hemorrhage

- **Capillaritis at the alveolar level**
- **Presentation – patients might only have one of these**
  - o **Dyspnea**
  - o **Hypoxemia**
  - o **Hemoptysis**
  - o **Anemia**
  - o **Alveolar infiltrates on imaging**

  → Can be life-threatening



De Lassence A. AJRCCM 1995;151:157

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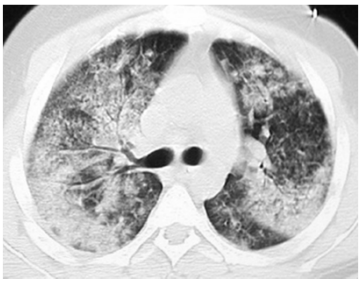
  - o **Alveolar infiltrates on imaging**

  → Can be life-threatening
- **Bronchoalveolar lavage**
  - o **Progressive bloody return on BAL**
  - o **>20% Hemosiderin laden macrophages**

  These findings are not specific for vasculitis



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ENT Features

- Sinus
  - Chronic sinusitis
  - Sinus pseudotumors
- Nasal
  - Crusting
  - Epistaxis
  - Saddle nose deformity

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- Sinus
  - Chronic sinusitis
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- Nasal
  - Crusting
  - Epistaxis
  - Saddle nose deformity
- Hearing issues:
  - Sensorineural hearing loss
  - Recurrent otitis
  - Recurrent inner ear fluid
- Orbital pseudotumors – may impair vision

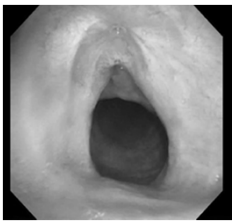
Airway Disease: "Asthma plus"

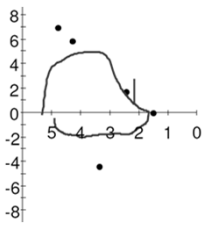
- **Peripheral eosinophilia**
- **Steroid dependence**
- **Severe concurrent sinusitis**
- **Transient pulmonary infiltrates**

→ Consider EGPA

Airway Disease: Stenosis

- **Subglottic stenosis**
  - **Shortness of breath or cough unresponsive to albuterol**
  - **Stridor**
  - **Fixed central airway obstruction**
    → blunting of both inspiratory and expiratory curves
  - **Expiratory disproportion index (EDI = FEV1/PEFR) >0.5 suggests clinically significant stenosis**





Reza Nouraei. Laryngoscope 2013; 123:3099-3104.
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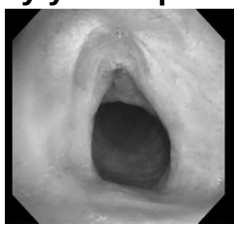
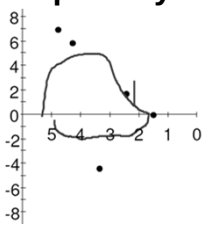
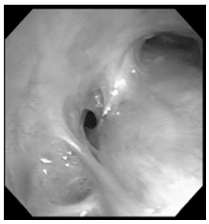
  - **Stridor**
  - **Fixed central airway obstruction → blunting of both inspiratory and expiratory curves**
  - **Expiratory disproportion index (EDI = FEV1/PEFR) >0.5 suggests clinically significant stenosis**
- **Large airway stenosis**
  - **Shortness of breath, focal wheeze**
  - **May yield biphasic expiratory curve or a "tail"**







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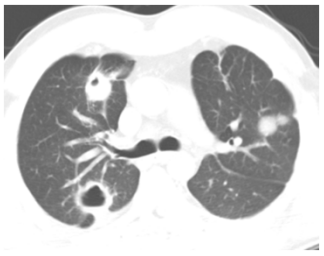
Pulmonary Nodules

- **May be solitary or multiple**
  - **When following typical guidelines with serial CTs, may increase in size quickly**
- **May be cavitary**
- **May be associated with adenopathy**

→Broad differential diagnosis, including infection and malignancy. BAL and biopsies can be helpful.



Interstitial Lung Disease

- **Relationship less clearly defined than with other manifestations, emerging data**
- **High resolution chest CT pattern may be nonspecific, or suggestive of usual interstitial pneumonia (UIP)**
- **Findings may precede other disease manifestations**
- **More commonly seen with positive anti-MPO**

Hosoda C, et al. Respirology 2016. 21:920-6.
Alba MA, et al. Autoimmunity Reviews 2017. 16(7):722-9.

Vasculitis: What The Primary Care Physician Needs To Know

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Renal Manifestations of AAV

Glomerulonephritis

- **Present in 18% of patients at initial presentation**
- **Around 80% of patients develop glomerulonephritis in the first 2 years after diagnosis.**
- **Can be the only presenting feature (renal-limited vasculitis)**
- **No specific presenting symptoms for glomerulonephritis but patients often have accompanying constitutional symptoms.**
- **If renal involvement is severe patients can present with uremic symptoms (nausea, vomiting, malaise, confusion) and oliguria**

Hoffman et al. Ann Intern Med. 1992;116(6):488

Glomerulonephritis

- **Often first detected with lab work, presentation varies in severity:**
  - **Rapidly progressive glomerulonephritis**
    - **Rapid worsening in renal function manifesting as an increase in creatinine a declining urine output**
  - **Mild increase in creatinine**
  - **Proteinuria (usually subnephrotic)**
  - **Hematuria**

Urine sediment

- **Evaluation of the urine sediment may show:**
  - **RBC casts**
  - **Acanthocytes**

Other Manifestations of AAV

Constitutional

- **Fatigue**
- **Fever**
- **Arthralgias**
- **Weight loss**

Cutaneous

- Leukocytoclastic angiitis
- Urticaria
- Livedo reticularis
- Thrombosis

Neurological and ophthalmic

- Mononeuritis multiplex
- Sensory neuropathy
- Cranial nerve abnormalities
- Central nervous system and orbital mass lesions
- External ophthalmoplegia
- Sensorineural hearing loss

Others

- **Gastrointestinal tract**
  - **Peritonitis**
  - **Bowel perforation**
  - **Bowel ischemia**
- **Heart**
  - **Pericarditis**
  - **Myocarditis**
  - **Conduction system abnormalities**

Clinical Presentation Depends on Severity

- **Inpatient**

Often due to capillaritis manifestations, may be organ or life-threatening

  - **Pulmonary-renal syndrome**
    - **Alveolar hemorrhage, glomerulonephritis**
    - **"Pan-consult"**
  - **Rapidly progressive renal failure**
    - **Significant rapid increase in creatinine**
    - **Symptoms of acute renal failure**

- **Outpatient**

Often due to granulomatous features

  - **Subglottic stenosis, asthma, sinusitis → cough, dyspnea**
  - **Pulmonary nodule**
  - **Saddle nose deformity**
  - **Otitis, sensorineural hearing loss**
  - **Microscopic hematuria, proteinuria**
  - **Mononeuritis → foot drop**
  - **Rash**
  - **Fatigue**
  - **Arthritis**

Diagnosis - Society guidelines

- **ACR criteria — The American College of Rheumatology (ACR) 1990 classification**
  - **Nasal or oral inflammation (painful or painless oral ulcers, or purulent or bloody nasal discharge)**
  - **Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities**
  - **Abnormal urinary sediment (microscopic hematuria with or without red cell casts)**
  - **Granulomatous inflammation on biopsy of an artery or perivascular area**
- **The presence of two or more of these four criteria yielded a sensitivity of 88 percent and a specificity of 92 percent**

Diagnosis – ANCA testing

- **ANCA**
  - **Indirect immunofluorescence testing**
    - **Sensitive, used for screening, cannot distinguish between disease based on positive ANCA**
    - **p-ANCA**
    - **C-ANCA**
  - **Immunoassays (ELISA, LUMINEX)**
    - **Specific, used for confirmation**
    - **Antibodies specific for antigens in neutrophil granules and monocyte lysosomes**
      - **MPO-ANCA**
      - **PR3-ANCA**

	PR3	MPO
C-ANCA	90%	10%
P-ANCA	10%	90%

Diagnosis – ANCA testing

- **ANCA positivity**
  - **GPA: 90% (80-90% of which is PR3-ANCA)**
    - **GPA without renal involvement: 60%**
  - **MPA: 90% (vast majority MPO-ANCA)**
  - **RLV: 75%**
  - **EGPA: 50% (70% of which is MPO-ANCA)**

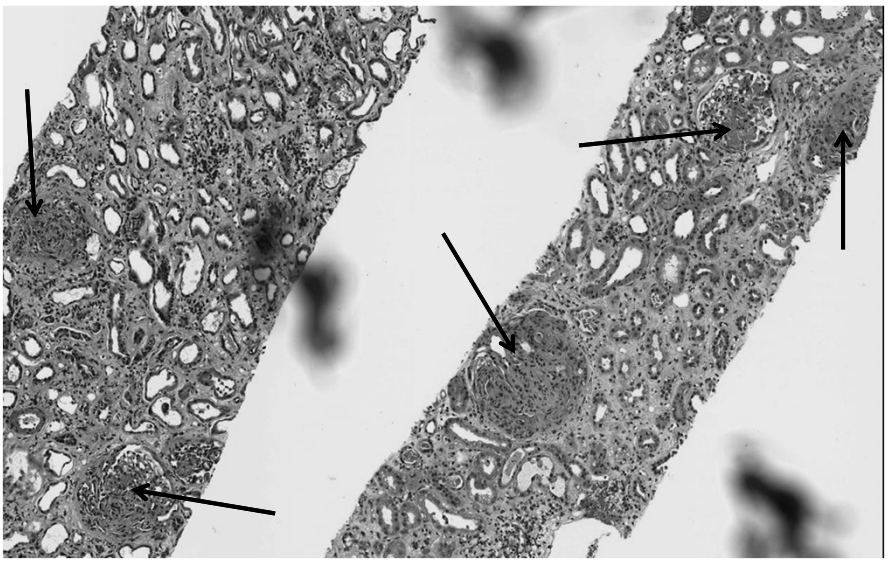
Hoffman et al. Ann Intern Med. Arthritis Rheum.1998;41(9):1521.
Guillevin et al. Arthritis Rheum. 1999;42(3):421.
Sablé-Fourtassou et al. Ann Intern Med. 2005;143(9):632.

Diagnosis – ANCA testing

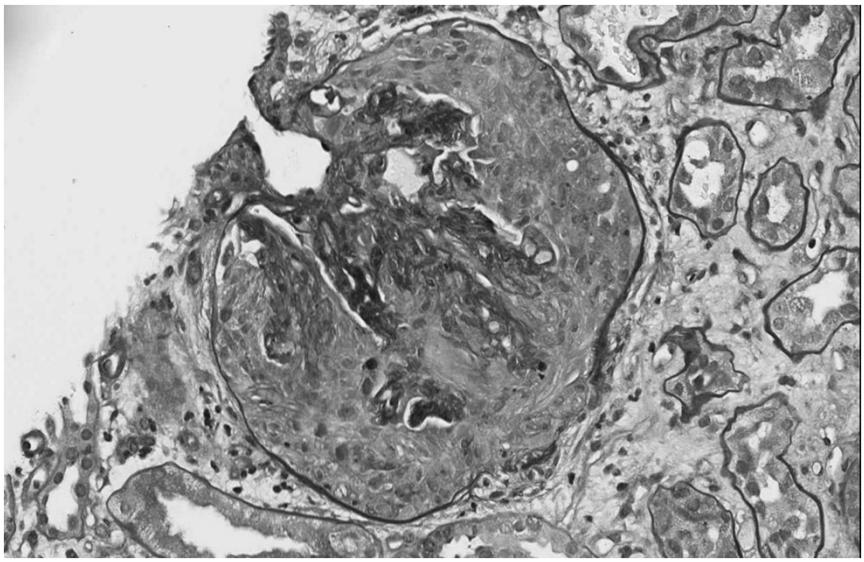
- **Other diseases with positive ANCAs:**
- **Drug-induced vasculitis (hydralazine, propylthiouracil, methimazole, carbimazole, minocycline, and levamisole)**
- **Other rheumatologic diseases:**
  - **Rheumatoid arthritis,**
  - **Systemic lupus erythematosus (SLE),**
  - **Sjögren's syndrome, inflammatory myopathies**
- **Gastrointestinal disorders:**
  - **Ulcerative colitis**
  - **Primary sclerosing cholangitis**
- **Cystic fibrosis**
- **Infection-associated glomerulonephritis (around 25%)**

Diagnosis – Kidney biopsy

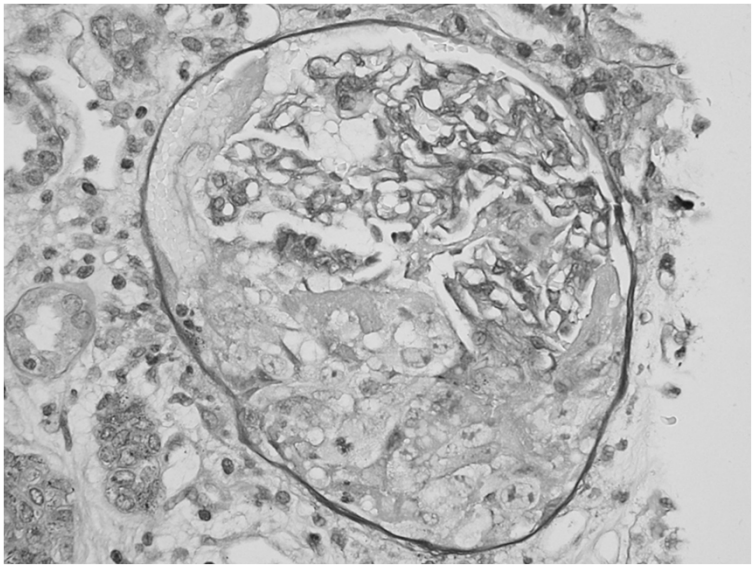
- **Proliferative glomerulonephritis**
  - **Often crescentic and necrotizing**
  - **“Pauci-immune” i.e. few or no immunoglobulin deposition.**



Glomeruli with crescents and necrosis (arrows). Also note the interstitial edema, mild inflammation and ATN. H&E



Large cellular crescent



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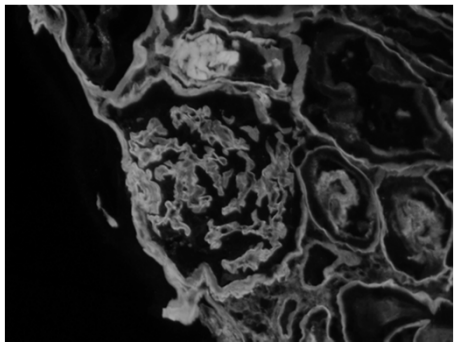
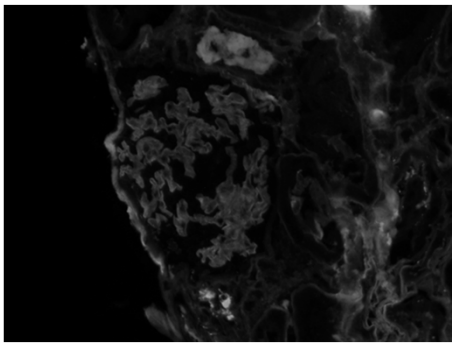
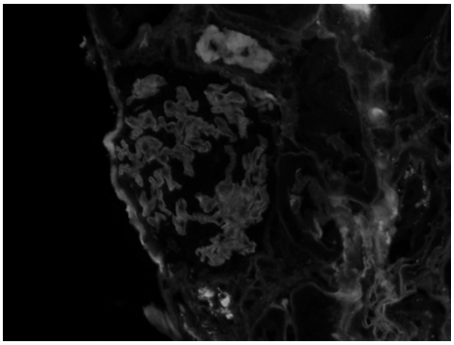


Albumin

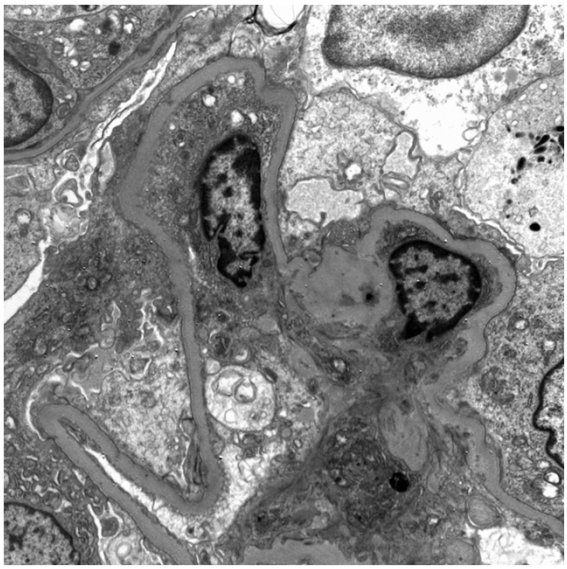


IgG



IgA

Negative IF



Unremarkable glomerular ultrastructure.
No deposits were seen.

Diagnosis – Other biopsies

- **Sinus, airway, lung, skin**
- **Pathologic features, key terms**
  - **Necrosis**
  - **Giant cells**
  - **Vasculitis**
  - **Capillaritis**
  - **Microabscess formation**
  - **Granulomatous inflammation**
  - **Palisading histiocytes**

Daum et al. Am J Resp Crit Care Med 1995;151:522-6.

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Treatment GPA & MPA

- **Initial therapy depends on severity of presentation**
  - **Severe disease = organ or life-threatening, often includes a capillaritis manifestation**
  - **Nonsevere disease = none of the above**
- **Phases of therapy**
  - **Remission induction**
  - **Maintenance of remission**

Daum et al. Am J Resp Crit Care Med 1995;151:522-6.

Treatment GPA & MPA – Remission Induction

	Nonsevere	Severe
Induction agent	Methotrexate Mycophenolate Azathioprine Rituximab	Cyclophosphamide OR Rituximab
Corticosteroid	Prednisone 0.5 mg/kg tapered over 6 months	Methylprednisolone 1g IV x 1-3 doses, Prednisone 0.5-1mg/kg tapered over 6 months
Other	Directed therapies	Plasma Exchange

****The only FDA approved medication is Rituximab***

Treatment GPA & MPA – Maintenance

- Azathioprine
- Mycophenolate
- Rituximab, evolving data
- Prednisone

Treatment of EGPA

- If there are true “vasculitic” manifestations, same agents are typically used for remission induction
- Mepolizumab (anti-IL-5) recently approved by the FDA
  - Depletes eosinophils
  - Subcutaneous injection, monthly
  - 300mg dose vs. 100mg dose for eosinophilic asthma
- Continue to aggressively treat asthma, triggers

Outcomes of Treatment GPA, EGPA, MPA

- **Good news: Remission is achieved in approximately 90% of patients**
- **Bad news: More than half of patients with severe disease go on to experience relapse**

Predictors of Relapse

Consistent Predictors of Relapse	Hazard Ratio
C-ANCA/PR3	1.8 (1.1,2.9)
Lung involvement	2.2 (1.4,3.6)
Upper respiratory involvement	1.6 (1.1,2.5)
All of the above	3.4 (2.1,5.7)
Any one of the above	1.8 (1.0,3.5)

Hogan et al. Annals Int Med. 2005 Nov 1;143(9):621-312005

Treatment: Nonpharmacologic Interventions

- **ENT**
  - **Sinus surgery, particularly with EGPA**
  - **Laryngoscopy**
  - **Airway laser**
- **Interventional Pulmonary**
  - **Stent placement**
  - **Balloon dilatation**
  - **Role in active disease vs. “damage” related to prior inflammation**

Contraception:

- **Risks for vasculitis patients and benefits need to be considered**
  - **IUD: increased risk of upper genital infections**
  - **Oral contraceptive pill containing estrogen:**
    - **Increased risk of thrombosis**
  - **Depo-provera injections and progestin-only pills are available**

Bone Health

- **Treatment and prevention of osteoporosis is problematic for vasculitis patients on chronic corticosteroids**
  - **Calcium and vitamin D**
- **Long term effects of bisphosphonates on future fetal growth are unknown**
- **Use of estrogen is associated with increased risk of flares in some studies**

Diet and Exercise

- **Heart healthy diet**
- **Moderate exercise has significant beneficial effect**

Infection prevention/monitoring

- Vigilance in evaluating suspected infectious processes
- Vaccination
  - Live virus vaccines: may be contraindicated depending on the medications the patient is on
- Vigilance with screening studies
- Use prophylaxis while on aggressive immunosuppressive regimen
  - Pneumocystis prophylaxis
  - Important to note that rituximab may remain active/present for >6 months, and may not always be captured on patient's EMR medication list

Autoimmune Diseases at a Glance

- Spectrum of diseases that vary from organ specific to systemic
- Almost every organ can be involved
- Autoimmune diseases' clinical manifestations can evolve over time
- A patient may have multiple autoimmune diagnoses

Autoimmune Diseases at a Glance

- **Therapy is only partially driven by data and the guidelines are largely consensus based**
- **Comorbidities are multiple and require vigilance**