Case 1: History

- A 45-year-old man presents with severe dyspnea and cough. He was in excellent health until 4 weeks ago when he developed a sore throat and fever. Over the past 2 weeks, he has noticed reddish ulcers on his legs, episodes of dark urine, and migratory arthralgias. He reports a past history of heavy alcohol use and acknowledges occasional “recreational” drug use.

Case 1: Objective Findings

- Diffuse pulmonary rales and rhonchi
- No detectable heart murmurs or $S_3$
- Palpable ulcerative rash over the legs
- No synovitis
- Hgb = 9.8; WBC = 23,000; ESR = 68; Creatinine = 2.8
- UA = 50 RBCs with casts
- Oximetry = 85% O$_2$ saturation
Approach to Multisystem Inflammatory Disease

• How should you approach a patient who presents with multisystem inflammatory disease?

Diagnostic Considerations in Patients With Multisystem Inflammation

• Systemic lupus erythematosus (SLE)
• Systemic vasculitis
• Vasculitis mimics

Diagnostic Classification of Vasculitis: What’s New and What’s Not

• Large Vessel-Takayasu (aorta and branches), Giant Cell (cranial branches)

• Medium Vessel- Polyarteritis nodosa, Kawasaki (coronary arteries), isolated Central nervous system
Diagnostic Classification of Vasculitis—II

- Small-vessel involvement with immune complex deposition
  - Hypersensitivity vasculitis
  - Henoch-Schönlein purpura
  - Behçet’s syndrome
  - Cryoglobulinemia—usually from Hepatitis C
  - Vasculitis of rheumatic diseases (SLE, RA)
  - Vasculitis secondary to viral disease: HepB,C, HIV,EBV, Paro, CMV


Diagnostic Classification of Vasculitis—III

- Small-vessel involvement without immune complex deposition (pauci-immune)
  - GPA (granulomatosis with polyangiitis), formerly Wegner’s
  - Churg-Strauss vasculitis
  - Microscopic polyangiitis


The Importance of the Name

- Granulomatosis with polyangiitis (formerly Wegener’s, now GPA)
- Microscopic polyangiitis (MPA)
- ANCA-Positive Vasculitis (APV)
- ANCA-Associated Vasculitis (AAV)
- Systemic Necrotizing Vasculitis (SNV)
Redacting the Use of “Wegener” Eponym

• Substantive evidence uncovered linking Dr. Friedrich Wegener to the Nazi regime:
  – Membership in the Sturmabteilung (“brown shirts”)
    • Early adoption of Nazi philosophy (1932)
  – Medical director of region in Portland near Lodz Ghetto
    • Inconceivable that he did not know of atrocities occurring in ghetto and his own department

ANCA Vasculitides

• Wegeners-90% ANCA +, most PR3
• Microscopic polyangitis-70% ANCA +, most MPO
• Churg-Strauss-~50% ANCA, both PR3 and MPO, with slight predilection for MPO
• Renal Limited Vasculitis-majority ANCA +, 75-80% MPO, indistinguishable from WG.MPA on histo
• Drug induced-usually MPO, some offending agents are hydralazine, PTU, minocycline, methimazole

Clinical Features Suggesting Vasculitis

• Multisystem inflammatory disease
• Rapidly progressive major organ dysfunction
• Constitutional symptoms (fever, weight loss)
• High ESR, severe anemia, thrombocytopenia
• Evidence of small-vessel inflammation:
  – In the kidneys = active urinary sediment
  – In the lungs = hemoptysis, dyspnea
  – In the skin = palpable purpura/hemorrhage
• Acute neurologic changes
  – Footdrop
  – Altered mental status
**Laboratory Tests That Are Helpful in the Diagnosis of Vasculitis**

- Tests suggesting immune complex formation and/or deposition
  - Rheumatoid factor and cryoglobulins
  - Antinuclear antibodies (ANA)
  - Low C3 or C4 levels
- Tests suggesting necrotizing vasculitis without immune complex deposition
  - Antineutrophil cytoplasmic antibodies (ANCA)
- Tests suggesting systemic inflammation
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)

**Diagnostic Approach to Patients With Suspected Vasculitis**

- Consider tissue biopsy of affected organ to determine
  - Vessel size
  - Histologic features of vessel inflammation
    - Vessel wall necrosis
    - Granulomas/giant cells
    - Immune complex and/or C3 deposition
- Consider angiography of mesenteric or cerebral vessels as clinically indicated

**What is ANCA-Associated Vasculitis?**

ANCA-associated vasculitis

Term used by some investigators to group

Based on

- High frequency of ANCA
- Similarity of some clinical features
- Shared involvement of small vessels

Differing opinions exist regarding the utility and benefit of this term

Take home messages:

- ANCA-associated vasculitis is not a separate disease from GPA/MPA
- ANCA does not have to be present to make a diagnosis
- The presence of ANCA does not confirm the diagnosis
Microscopic Polyangiitis

Historical Background

1866 Kussmaul & Maier – description of “periarteritis nodosa”

1948 Davson - glomerular and small vessel disease in PAN “microscopic polyarteritis”

1994 Chappel Hill Consensus Conference

<table>
<thead>
<tr>
<th>Polyarteritis Nodosa</th>
<th>Microscopic Polyangiitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium Vessels</td>
<td>Small vessels</td>
</tr>
<tr>
<td>No lung involvement</td>
<td>Pulmonary hemorrhage</td>
</tr>
<tr>
<td>No glomerular involvement</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Relapses uncommon</td>
<td>Frequent relapses</td>
</tr>
<tr>
<td>Not associated with ANCA</td>
<td>ANCA associated (MPO)</td>
</tr>
</tbody>
</table>

Microscopic Polyangiitis

Diagnosis

Differential:
• other cause of pulmonary-renal syndrome
  – anti-GBM disease (Goodpasture’s)
  – systemic lupus erythematosus
  – post-streptococcal glomerulonephritis
• infections
• neoplasm

Diagnosis base on:
• consistent clinical features
• compatible histologic findings

Churg-Strauss Syndrome

Thought of as having 3 phases
(not seen in all patients)

Prodromal phase: asthma, allergic rhinitis

Eosinophilic phase: peripheral eosinophilia
eosinophilic tissue infiltrates

Vasculitic phase: nerve, skin, lung, gi tract, heart
Churg-Strauss Syndrome Diagnosis

Differential:
• hypereosinophilic syndrome
• neoplasm / eosinophilic leukemia
• granulomatous disease
• infection
  - mycobacteria
  - parasites

Diagnosis based on:
• asthma
• peripheral eosinophilia > 1500 / mm3
• systemic vasculitis involving 2 or more extrapulmonary organs
  (Guellevin et al. 1999 – manifestations consistent with vasculitis)

ANCA associated vasculitis

Clinical Features

• Conceptualizing diseases by vessel size can be useful but is not absolute
• GPA and MPA predominantly affect the small- to medium-sized vessels
• Typically without immune complexes, ie. pauci immune

• Different - GPA and MPA are phenotypically different diseases

  GPA
  - Necrotizing, destructive upper airways disease
  - Cavitary lung disease
  - Orbital lesions
  - Subglottic and endobronchial stenoses

• Similar - GPA and MPA share certain features and challenges

  GPA and MPA
  - frequent presence of circulating ANCA
  - potential for life-threatening disease (lung and kidney)
  - high rate of relapse
  - need for aggressive immunosuppression for severe disease

Wegner’s no more: Granulomatosis with Polyangiitis (GPA)

• Granulomatosis with polyangiitis (GPA) primarily involves the upper and lower respiratory tracts and the kidneys
• "Limited" form have clinical findings isolated to the respiratory tract - can occur in ¼ of cases, although 80% may go on to develop glomerulonephritis. Specifically, pts with limited disease are younger at disease onset, and more likely to be women.
**Granulomatosis with Polyangiitis (GPA)**

- Renal involvement is manifested by acute renal failure with red cells, red cell and other casts, and proteinuria.
- Pts with microscopic polyangiitis have a renal lesion that is essentially indistinguishable from that of pts with classic GPA; the principle difference is the absence of granulomatosis inflammation, although some experts consider the presence of any significant upper respiratory tract involvement to be indicative of GPA.

**Renal Manifestations of WG and MPA**

- Glomerulonephritis, often presenting as rapidly progressive glomerulonephritis, is frequent in AAV.
- Pathologically, this is indistinguishable in WG, MPA and renal-limited disease.

*Image courtesy of Dr. J. Charles Jennette*

**Endothelium and Vascular Wall Damage**
Endothelium and Vascular Wall Damage

Reactive oxygen species, proteolytic enzymes, and factors that activate the alternative complement pathway are thought to be released, causing damage to the endothelium and vascular wall.

Granulomatosis with Polyangitis (GPA) and Microscopic Polyangiitis (MPA)

Polyangitis with Granulomatosis(GPA) and Microscopic polyangiitis (MPA) are two forms of ANCA-associated vasculitis.

- Damage to vessel walls may lead to:
  - Decreased organ perfusion and ischemia
  - Hemorrhage
  - Impairment of organ function

- Immunofluorescence typically shows little to no deposition of immune complexes (pauci-immune).

Key Manifestations of PGA and MPA

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary Infiltrates/ Nodules</th>
<th>Alveolar Hemorrhage</th>
<th>Glomerulonephritis</th>
<th>Upper Airway Disease</th>
<th>Skin Purpura</th>
<th>Peripheral Nervous Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>WG</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>MPA</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

GPA: Other Manifestations

- Upper and lower airways, including subglottic region or trachea
- Joints (myalgias, arthralgias, arthritis)
- Eyes (conjunctivitis, corneal ulceration, episcleritis/scleritis, optic neuropathy, nasolacrimal duct obstruction...)
- Skin (hemorrhagic lesions, palpable purpura)
- Nervous system (cranial nerve abnormalities)
- GI tract/Heart, lower GU

GPA: Pathogenesis

- Production of ANCA (anti-neutrophil cytoplasmic antibodies) is one of the hallmarks of WG and related forms of vasculitis (Churg-strauss, MPA, pauciimmune glomerulonephritis, drug-induced).
- ANCA are directed against antigens present within the primary granules of neutrophils and monocytes, and thus produce tissue damage via interactions with primed neutrophils and endothelial cells.
- ~90% of pts with active generalized WG are ANCA positive, but some do not have ANCA, and those with limited forms of the dz, up to 40% may be ANCA negative, thus the absence of ANCA does not exclude the diagnosis of Wegener’s.

GPA: Pathogenesis

- Most common targeted antigens in Granulomatosis with Polyangiitis
  - Proteinase 3 (PR3), observed in 70-80% of pts
  - Myeloperoxidase (MPO) - target in approximately 10%
  - Dual positivity is rare and, and generally indicated the presence of another condition such as SLE
  - ~70% of pts with MPA are ANCA positive and most have MPO-ANCA, with only a minority having PR3
GPA: Presentation

- Most common presenting symptoms include persistent rhinorrhea, purulent/bloody nasal discharge, oral and/or nasal ulcers, polyarthralgias, myalgias, or sinus pain.
- Less common are hoarseness, stridor, earache, conductive and sensorineural hearing loss or otorrhea
- Frequent early complaints of lower tract include cough, dyspnea, hemoptysis, pleuritic pain
- Nonspecific complaints of fever, night sweats, anorexia, weight loss, and malaise
- Renal involvement – ACTIVE URINE SEDIMENT (microscopic hematuria w/ or w/o red cell casts) and variable degrees of renal insufficiency

GPA: Diagnosis

- Presence of 2 or more yield 88% sensitivity and 92% specificity
  - Nasal or oral inflammation
  - Abnormal chest radiograph (nodules, alveolar opacities)
  - Abnormal urine sediment
  - Granulomatous inflammation on biopsy of an artery or perivascular area

GPA: Diagnosis

- Routine Labs-nonspecific- Leukocytosis, thrombocytosis (>400,000), marked ESR, and normocytic, normochromic anemia, mildly elevated RF
- ANCA- as previously described
- Tissue Biopsy- dx should be confirmed by tissue bx at site of active disease
  - Nasopharyngeal bx less invasive, but may not see full pathogenesis due to small amount of tissue- acute and chronic inflammation
  - Renal bx segmental necrotizing glomerulonephritis w/ or w/o crescents
  - Skin-leukocytoclastic vasculitis with little or no complement and immunoglobulin
  - Lung-granulomatous and vasculitis
GPA Wegener’s Diagnosis - Biopsy

Not all biopsies are diagnostic
• Changes are patchy
• Positive yield associated with the amount of tissue obtained

ENT 21% sinuses > nasal membrane > subglottis
Lung 91% open lung biopsy
7% transbronchial biopsy
Kidney focal, segmental, necrotizing glomerulonephritis with few to no immune deposits (pauci-immune)
Skin usually insufficient evidence for diagnosis
cutaneous vasculitis can be seen in many settings

C-ANCA staining pattern of ethanol-fixed normal human neutrophil

Antineutrophil Cytoplasmic Antibodies

• ANCA by immunofluorescence methods
  – c-ANCA = Wegener’s disease (60% to 90%)
  – p-ANCA = microscopic polyangiitis (MPA) (50% to 80%), UC (40% to 80%), Crohn’s (10% to 40%)

Antineutrophil Cytoplasmic Antibodies

- ANCA by ELISA methods
  - Proteinase 3 (PR3) = Wegener’s disease
  - Myeloperoxidase (MPO) = MPA

ANCA Testing

Must combine IF and ELISA

C-ANCA IF + anti-PR3 = Diagnostic C-ANCA/aPR3+

P-ANCA IF + anti-MPO ab = Diagnostic P-ANCA/aMPO+

- IF alone, ELISA alone, or any other combination is NOT diagnostic and not reliable
- Standard or care

Anti-Neutrophil Cytoplasmic Autoantibodies (ANCA)

- ANCA Specificity (for AAV) is >95%
  - If the proper testing system is used
  - If the appropriate clinical setting exists

- ANCA Sensitivity (for vasculitis):
  - GPA (WG)-non-renal: >80% ANCA+
  - GPA (WG)-renal: 90% ANCA+ (mostly C/αPR3)
  - MPA: 90% ANCA+ (mostly P/αMPO)
  - CSS: ~40% (associated with renal disease)
Frequency of ANCA* in PGA and MPA

*Not all patients are ANCA-positive

Remember ANCA’s are not always present

- Can certainly have GPA or MPA (less likely) or CSS (commonly) without ANCA, esp. if non-renal or non-alveolar hemorrhage
- False positives do occur
- Still need biopsy if:
  - Suspect GPA/MPA and ANCA-negative
  - ANCA+ but not clearly vasculitis
  - Diagnosis established but still concerned about infection/tumor

ANCA-Associated Vasculitis

Clinical Features

- Upper airway disease
  - Nasal
  - Paranasal sinus
  - Subglottic stenosis
- Pulmonary disease
  - Nodules
  - Alveolitis/capillaritis
  - ILD/fibrosis
  - Other
- Glomerulonephritis
- Neuropathy
  - Sensory
  - Motor
  - Olfactory
  - Visual
- Arthritis/Articularis
- Malaise/Fatigue
- Eye Disease
  - Scleritis/hypopyon
  - Panuveitis
- Skin/Mucosa
  - Oral ulcers
  - Purpura
  - Nodule
- Vascular
  - Gangrene
  - Venous thrombosis
- Cardiac Disease
- GI Disease
- Laboratory Findings
  - ANCA
  - Nephrotic syndrome
  - Elevated ESR/CRP
  - Anemia
- Other
### Diseases That Can Mimic Vasculitic Syndromes

**Vasculitis**
- Infectious diseases
  - Bacterial endocarditis
  - HIV infections
  - Viral hepatitis
- Paraneoplastic syndromes
- Atrial myxoma

**Vasculopathy**
- Cholesterol emboli syndrome
- Toxic drug effects
  - Ergots
  - Cocaine
  - Amphetamines

### Major Vasculitis Mimics
- Embolic disease
- Thrombotic disease
- Vasospasm, vasoconstriction, vasoocclusion
- Malignancy
- Infection
- Drug/toxin reactions
- Other vasculopathies
- Other systemic inflammatory diseases
- Other other (miscellaneous)

### Medications for Vasculitis May mimic Vasculitis
- Cyclophosphamide
  - Hematuria mimicking active renal disease
  - Aneurysms
  - Bladder carcinoma
  - Infections
  - Cardiomyopathy (rare)
- Methotrexate
  - Intestinal lung disease
  - Oral Ulcers
- Azathioprine
  - Hyperamylasemia syndrome
  - Fever, aseptic meningitis
- Glucocorticoids
  - Hypertension
  - Glucocorticoid withdrawal
  - Aneurysms
  - Fatigue
  - Fever
  - Anti-TNF agents
  - Drug-induced lupus
- TMP/SMX
  - Rise in creatinine (not GFR)
  - Rash
- Dapsone
  - Methemoglobinemia → Hypoxemia
  - Methemoglobinemia
Studies Useful in Diagnosing Vasculitis Mimics

• Blood culture
• Viral hepatitis antigen/antibodies
• HIV test
• Urine toxicology screen
• Angiography
• Echocardiogram

Red Flags for Vasculitis Mimics

• Presence of a heart murmur
• Necrosis of lower extremity digits
• Splinter hemorrhages
• Prominent liver dysfunction
• History of recreational drug use
• History of high-risk sexual activity
• Prior diagnosis of neoplastic disease
• Unusually high fevers

Cocaine-Induced Midline Destructive Lesions (CIMDL) Mimics GPA with + ANCA

• CIMDL clinically mimics limited granulomatosis with polyangitis (GPA): more severe local destruction, less systemic symptoms, no other organs involved.
  Trimachi et al, Medicine 2001; 80:391-404
• P-ANCA positive, MPO-ANCA negative, possibly PR3-ANCA positive (50%), HNE-ANCA positive.
• HNE-ANCA and PR3-ANCA are not cross-reacting antibodies, but co-existing antibodies.
  Peikert et al, Arthritis Rheum 2008; 58:1546-51
### Levamisole Complicates Matters Even More

- Veterinary antihelminthic
- Immune-Modulator
- Increase dopamine levels in the brain
- Ear lobe necrosis
- Skin necrosis and vasculitis (microthrombi, thrombotic vasculopathy)
- Agranulocytosis
- Anti-phospholipid antibodies
- ANCA are common, directed again multiple antigens

### WHAT ABOUT BEHCET’S??
**INTERNATIONAL STUDY GROUP CRITERIA FOR BEHCET’S DISEASE**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent oral ulceration</td>
<td>Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month period</td>
</tr>
<tr>
<td>Plus 2 of:</td>
<td></td>
</tr>
<tr>
<td>Recurrent genital ulceration</td>
<td>Aphthous ulceration or scarring observed by physician or patient</td>
</tr>
<tr>
<td>Eye lesions</td>
<td>Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions; or Acneiform nodules observed by physician in postadolescent patients not on corticosteroid treatment</td>
</tr>
<tr>
<td>Positive Pathergy test</td>
<td>Read by physician at 24 to 48 hours</td>
</tr>
</tbody>
</table>


### Work-up for AAV Baseline Evaluation

- Careful Medical History and Physical
- Pertinent labs
- Urinalysis (if dip+, you must do proper micro)
- ANCA
- Chest x-rays
- As needed (often are):
  - Chest and sinus CTs
  - ENT exam (trachea) and CTs
  - Audiogram
- Biopsy
- Sometimes: nerve conduction tests
- Don’t miss co-morbidity (esp. infection)
- Exclude vasculitis mimics: Hep C, HepB, SBE, etc
Confirming the Diagnosis of AAV

- Often (but not always) requires biopsy
  - Balance between risk and yield among sites
- Need an experienced pathologist
- ANCA may substitute in some settings
- Rule out infections (esp. in recurrent disease)
- Need to consider the whole picture

Establishing a Diagnosis or Flare of Vasculitis

- Do NOT assume vasculitis without pathognomonic findings or diagnostic histologic evidence
- When in doubt, re-look at everything
  - Especially pathology specimens and angiograms
  - “When you with not to miss, then tissue is the issue”
  - Almost never wrong to look for infection or malignancy
- It’s OK to NOT treat when uncertainty exists
  - You will be wrong sometimes
  - You may do more damage overall with assumption of vasculitis and treatment

- Only the pairs of...
  - C-ANCA / PR3-ANCA and
  - P-ANCA / MPO-ANCA
  - have a high diagnostic specificity (positive predictive value) for ANCA-associated vasculitis.
- Single modality testing is much more likely to provide misleading results for...
  - Methodological reasons (trade-off of analytical sensitivity versus specificity)
  - Clinical reasons (more “true false-positives”)
Case 2: Clinical History and Exam

- A 51-year-old man is seen for complaints of hives, skin rash, and ulcers over his shins
- Physical exam reveals
  - Palpable purpura, ulcers, and urticarial lesions over the arms and legs
  - Palpable cervical and axillary adenopathy
  - Hepatosplenomegaly

Case 2: Diagnostic Studies

- Laboratory studies
  - ESR = 64; RF = 489 iu; C3 = 24; AST = 876; ALP = 234
  - UA shows 20 to 30 RBCs, negative protein, no casts
  - Cryoglobulins = positive
- Skin biopsy reveals leukocytoclastic vasculitis
- ANCA and ANA negative

Case 2: Question

- What is the most probable etiology for this vasculitic syndrome?
  A. Parvovirus infection
  B. Drug reaction
  C. Hepatitis C infection
  D. Staph sepsis
CASE 2: Answer

- C. Hepatitis C infection

Essential
cryoglobulinemic vasculitis is not so essential
anymore!

Hepatitis C Virus-Associated Vasculitis

- The cause of most cryoglobulinemic vasculitis
- Cryoglobulins lead to tissue damage
- Patients are rheumatoid factor positive
- Prednisone and/or cytotoxic agents may increase virion load
- Alpha interferon with antiviral therapy may improve vasculitis and infection
- Despite therapy, relapses are common


Hepatitis B Virus-Associated Vasculitis

- Seen in 10% to 50% of polyarteritis nodosa cases
- Presents as a systemic vasculitis with abnormal liver function tests
- Tissue damage is due to immune complexes
- Therapy includes steroids, antiviral agents, and occasionally apheresis
**HIV Virus-Associated Vasculitis**

- Masquerades as many rheumatic syndromes
  - Polyarteritis nodosa
  - Churg-Strauss vasculitis
  - Hypersensitivity vasculitis
  - Systemic lupus erythematosus
  - Sjögren’s syndrome
  - Primary CNS vasculitis

- Primary therapy is antiviral
- Careful use of immunosuppressive agents may be considered


**General Concepts About Vasculitis Treatment**

- Tissue damage with vasculitis requires early diagnosis and treatment
- Combinations of high-dose steroids and cytotoxic drugs are first line therapy
- Effective treatment can improve outcome
- There is a delicate balance between treatment efficacy and toxicity
- Well-defined clinical outcomes are needed to guide the intensity and duration of treatment

**Glucocorticoids are KEY for Acute Treatment of ANCA+ Vasculitis**

- Glucocorticoids are what save lives and kidneys in short-term
- Don’t delay when pulmonary hemorrhage or RPGN suspected
- Can usually wait until patient more stable to start other immunosuppressives
Standard Therapy for Systemic Necrotizing Vasculitis

Initial therapy

**Glucocorticoids:** Prednisone 1mg/kg/day

**Cyclophosphamide:** 2 mg/kg/day

For critically ill patients

**Glucocorticoids:** 1 gram methylprednisolone daily for 3 days

**Cyclophosphamide:** 3-5 mg/kg/day I.V. for 2-3 days, then 2 mg/day

F/U Therapy for Systemic Necrotizing Vasculitis

Treatment following partial or complete remission

**Glucocorticoids:** Taper to an every other day schedule as clinically tolerated

**Cyclophosphamide:** Less toxic agent for f/u, but when

Monitoring

- CBC with differential every 2-4 weeks once stable
- Urinalysis monthly once stable
- Monitor every 3-6 months indefinitely
- Rising ANCA titers may precede relapse

Pulse vs Oral Cyclophosphamide?

- Pulse
  - Good remission agent
  - Less bladder toxicity
  - Can be problematic
  - Varying renal function
  - Cytopenias in sick folks
  - Good if patient NPO or can’t take copious H2O
  - Higher relapse rate...
  - Note: CYCLOPS schedule is IV CYC q2-3 weeks, not monthly

- Daily Oral
  - Good remission agent
  - Likely more toxic
  - Easier to control cytopenias
  - Can start in hospital, (even as daily IV)
  - More convenient for patient

US vasculitis centers still use oral regimen more:
EU centers use IV more
**CYCLOPS IV cyclophosphamide regimen**

- 10 Pulses of 15 mg/kg
  - 2.5, >60yr
  - 2.5, creat >100
  - 5, >70yr

This is not the usual "NIH protocol"

Note the dose/frequency

**CYCLOPS: Conclusion**

Conclusion: The pulse cyclophosphamide regimen induced remission of ANCA-associated vasculitis as well as the daily oral regimen at a reduced cumulative cyclophosphamide dose and caused fewer cases of leukopenia.

---

**Rituximab Treatment of ANCA + Vasculitis RAVE Trial**

- A multicenter, randomized, double-blind, double-dummy, non-inferiority trial
- Compare Rituximab with standard cyclophosphamide (CYC) therapy for the induction of complete remission by 6 months in patients with severe WG (GPA) and MPA
  - Primary endpoint: Remission of disease (BVAS/WG(GPA) of 0) and successful completion of prednisone taper at 6 months
- Long-term follow-up (to 18 month common close-out date*)


---

**Measurements of Disease Activity**

**Birmingham Vasculitis Activity Score (BVAS)**

BVAS was originally developed and validated in 1994:
- Constructed by a consensus group of physicians
- Comprises 59 items in 9 organ systems
- Positive findings only recorded if attributable to disease
- Items weighted between 1 and 9 based on relative importance
- Overall range 0 to 63, with higher score representing more active disease
- Adopted by European Vasculitis Study Group (EUVAS) for its clinical trials
- Two revisions
  - BVAS version 2
    - Scored in 2 components—new/worse disease (BVAS1), persistent disease (BVAS2)
    - Latest iteration is BVAS version 3 (2009)—reduced items to 56 and a single persistent box for the whole form

Possible Role of B Cells in PGA and MPA

ANTIGEN

ANCAs (Anti-MPO, Anti-PR3)

Produce ANCA

Plasma cell

Produce proinflammatory cytokines

ACT AS APCs

Activated B cell

Antigen


RAVE Trial for Vasculitis

Study Design

Patients in Remission
AZA§ - placebo (daily up to 18 months)

Rituximab

Patients in Remission
AZA (2 mg/kg daily up to month 18)

Cyclophosphamide

Oral CYC placebo daily for 3–6 months

Prednisone (tapering)*

Rituximab placebo

IV (375 mg/m² weekly ×4)

Crossover allowed between study arms‡

Patients in Remission
AZA (2 mg/kg daily up to month 18)

CYC (Control Group)

Prednisone (tapering)*

Rituximab

Patients in Remission
AZA§ - placebo (daily up to 18 months)

CYC (2 mg/kg) daily for 3–6 months

Prednisone

Rituximab

IV (375 mg/m² weekly ×4)

Control Arm


RAVE Vasculitis Trial

Primary Endpoint: Complete Remission at 6 Months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nilotinib (n=99)</th>
<th>CYC (n=98)</th>
<th>Treatment Difference (Nilotinib - CYC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>64%</td>
<td>53%</td>
<td>11%</td>
</tr>
<tr>
<td>95.1% CI</td>
<td>65%, 73%</td>
<td>43%, 63%</td>
<td>-3%, 24%†</td>
</tr>
</tbody>
</table>

BVAS/WG = 0 and prednisone = 0 mg

CI: confidence interval
*Non-inferiority was demonstrated because the lower bound was higher than the pre-determined non-inferiority margin (-3% > -20%).
†This 95.1% CI reflects an additional 0.001 alpha to account for interim efficacy analysis.
RAVE Vasculitis Trial
Remission Regardless of Prednisone Use at 6 Months

<table>
<thead>
<tr>
<th></th>
<th>Rituximab (n=99)</th>
<th>CYC (n=98)</th>
<th>Difference In Rate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission*</td>
<td>80 (81%)</td>
<td>65 (66%)</td>
<td>14.5</td>
<td>0.02</td>
</tr>
<tr>
<td>95.1% CI</td>
<td>73, 87</td>
<td>60, 76</td>
<td>7.97</td>
<td></td>
</tr>
</tbody>
</table>

ITT population, worst case imputation
CI, confidence interval
* The proportion of patients who achieved a BVAS/WG of 0
† Two-sided χ² test

RAVE Trial: 18 Month Efficacy Data
Complete Remission Rates between Rituximab and CYC groups at 6, 12, and 18 Months (M)

<table>
<thead>
<tr>
<th></th>
<th>Rituximab (n=99)</th>
<th>CYC (n=98)</th>
<th>Difference*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6M</td>
<td>63 (63.6%)</td>
<td>52 (53.1%)</td>
<td>10.0%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(2.2%, 24.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12M</td>
<td>44 (44.4%)</td>
<td>37 (37.8%)</td>
<td>6.7%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(1.6%, 20.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18M</td>
<td>38 (38.4%)</td>
<td>30 (30.6%)</td>
<td>7.8%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(5.5%, 21.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Worst case imputation analysis
* Two-sided 95.1% CI

RAVE Trial: Infusion Reactions
Acute Infusion Reactions* During or Within 24 Hours of Initial Course of Therapy

Among the 99 patients treated with Rituxan, 12% experienced at least one infusion-related reaction, compared with 11% of the 98 patients in the cyclophosphamide group.

```
<table>
<thead>
<tr>
<th>Infusion</th>
<th>Rituximab (n=99)</th>
<th>CYC (Rituxan placebo) (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Second</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Third</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Fourth</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>
```

12% 7% 5% 4% 1% 2%

First Infusion Second Infusion Third Infusion Fourth Infusion

12% 7% 5% 4% 1% 2%
RAVE Trial: Infections and Serious Infections

- Infection was the most common category of adverse events reported
- The most common infections in the Rituximab group were upper respiratory tract infections, urinary tract infections, and herpes zoster
- The most common serious infection was pneumonia
- The rates of serious infections were approximately 25 (Rituximab-treated) and 28 (CYC-treated) per 100 patient-years

Rituximab treatment of ANCA + Vasculitis

- WG(GPA) and MPA are 2 forms of ANCA-associated vasculitis associated with antibodies (anti-PR3 and anti-MPO) believed to be involved in pathogenesis
- Treatment for WG(GPA) and MPA have been divided into induction and maintenance phases, with induction often involving the use of CYC for severe manifestations
- Rituximab is not inferior to cyclophosphamide for remission induction in patients with severe WG(GPA) and MPA

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

AKA: “RITUXVAS”

- 44 patients with AAV
- Demonstrated similar outcomes in renal disease
- 3:1 randomization (open-label) to
  - RTX + 2 doses of CYC at start
  - CYC (IV CYCLOPS regimen)

Jones et al
Methotrexate
For Induction of Remission

• Can effectively induce remission in non-organ/life-threatening disease
• Less toxic than cyclophosphamide
• Should push to high doses (25mg/week)
• Some patients with mild renal involvement may be treated successfully (controversial)
• Can not give to all patients
• Overall: remission rates appear lower, and relapse rates appear higher, compared to cyclophosphamide (MTX may still be good option)

Methotrexate: Remission Induction

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Remission</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sneller, 1995</td>
<td>42</td>
<td>71%</td>
<td>31%</td>
</tr>
<tr>
<td>De Groot, 1998</td>
<td>17</td>
<td>59%</td>
<td>NA</td>
</tr>
<tr>
<td>Stone, 1999</td>
<td>19</td>
<td>79%</td>
<td>50%</td>
</tr>
<tr>
<td>Langford, 2000</td>
<td>21</td>
<td>95%</td>
<td>55%</td>
</tr>
<tr>
<td>WGET, 2005</td>
<td>52</td>
<td>88%</td>
<td>24%</td>
</tr>
<tr>
<td>de Groot, 2005</td>
<td>51</td>
<td>90%</td>
<td>70%</td>
</tr>
<tr>
<td>Villa-Forte, 2007</td>
<td>25</td>
<td>88%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Studies vary in i) disease activity; ii) renal disease; iii) definitions of relapse; iv) length of follow-up

Maintenance with MTX or AZA
Post initial treatment with Cyclophosphamide

• 3-6 months CYC then MTX or AZA
• Has been standard of care for most patients with AAV and severe initial disease or flare
• Wait until prednisone dose is ≤ 20mg/day
• Decision between MTX or AZA influenced by co-morbidities (renal, hepatic) or lifestyle (alcohol)
• Emerging Data on MMF makes it 3rd choice after MTX and AZA
**Methotrexate for Remission-Maintenance**

(after initial remission with cyclophosphamide)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Groot, 1998</td>
<td>33</td>
<td>12%</td>
</tr>
<tr>
<td>Langford, 2000</td>
<td>31</td>
<td>18%</td>
</tr>
<tr>
<td>Rheinhold-Keller, 2002</td>
<td>71</td>
<td>37%</td>
</tr>
<tr>
<td>WGET, 2005</td>
<td>122</td>
<td>~25%*</td>
</tr>
<tr>
<td>Villa-Forte, 2007</td>
<td>57</td>
<td>65%</td>
</tr>
<tr>
<td>Pagnoux, 2008</td>
<td>59</td>
<td>~50%</td>
</tr>
</tbody>
</table>

* A few patients on AZA mixed in date

---

**Plasma Exchange for AAV: 2012**

- If anti-GBM+ then use PLEX even if also ANCA+
- Consider use for severe renal disease
  - MEPEX trial (Methylprednisolone vs Exchange)
  - First wait for a few days?
  - 7 sessions as per MEPEX
- Consider use for severe alveolar hemorrhage
  - BUT REALIZE THERE ARE NO DATA!
- Use in conjunction with glucocorticoids and immunosuppressive agents

---

**MEPEX – Main Entry Criteria**

**Plasma exchange vs Pulse Methylprednisone**

- Biopsy-proven, ANCA+, WG, MPA or renal-limited vasculitis
- New-onset active necrotizing glomerulonephritis with creatinine >500μmol/l (5.7 mg/dl) and/or oliguria/dialysis
- All patients received oral cyclophosphamide

**MEPEX – Main Exclusion Criteria**

- Alveolar hemorrhage requiring ventilation
- Anti-GBM antibodies
- Dialysis > 2 weeks prior to entry

Jayne et al. JASN 2007
Plasma exchange vs Pulse Methprednisolone: MEPEX

Conclusions
• Increased chance of renal recovery in renal failure due to AAV by addition of plasma exchange to oral CYC and GCS compared to the addition of IV MP
• High mortality and severe adverse event rate, but not significantly different between groups

Caveats
• Patients with alveolar hemorrhage were excluded
• Only patients with very severe renal disease enrolled
• Mortality rate extremely high
• Generalizability is unclear

Jayneet al. JASN 2007

Follow-Up for AAV
• Reevaluate patients at key intervals:
  • Time of Flare
  • End of remission inductions period
  • End or remission-maintenance therapy
• Suggested intervals:
  • Clinical Visits every 3 months
  • Labs every 1-3 months
  • Disease monitoring
  • Drug toxicity monitoring
  • Urinary dipstick monthly at home by patient?
  • CD19 counts?
• Patient and family education:
  • What to look for and when to call
  • Be on the look out for infection vs flare

Persistent ANCA and ANCA levels in relapsing disease?

• Do ANCA levels correlate with disease activity?
• Do ANCA increases predict relapses?
• Should ANCA Changes be used to guide treatment?
Can ANCA Titers be Used to Guide Therapy Decisions?

- Controversial
- Earlier date indicated YES, but...
  - Study sample sizes small, retrospective data
  - Benefit of ANCA-based Rx not proven
- More recent data indicates ANCA titers do NOT reliably predict flares
- Advise against using ANCA titers to determine need to change therapy
- Future new ANCA testing approaches may change outlook but not yet

Treatment of AAV: Unmet Needs

- Less toxic regimens
  - CYCLOPHOSPHAMIDE sparing/avoiding
  - Glucocorticoid-sparing
  - Non-sterilizing & non-steratogenic drugs
  - Reduction in infections
- Prevention of relapse
  - Relapse rates are high, even on treatment
- Treatment of exceptionally resistant disease
- Treatment of mild-moderate disease
  - Especially smoldering ENT problems
- Advances in non-drug therapies
  - For sub-glottic stenosis, Retro-orbital surgery, bronchial stents

Points to Remember

- When a patient has a complex multisystem inflammatory picture—think vasculitis
- If a vasculitic disorder is considered, search for its cause
- Employ tests and biopsies when indicated, but remember to treat the patient, not the test
- Rapid diagnosis and treatment is often organ or lifesaving
- Consider viral associated rheumatic/vasculitis syndromes when the autoantibody results are not typical