Pulmonary Vasculitides

Manuela Cernadas, M.D.

Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

BWH BRIGHAM AND WOMEN'S HOSPITAL

Mass General Brigham

HARVARD MEDICAL SCHOOL
TEACHING AFFILIATE

Conflict of Interest/Affiliation Disclosure Statement

I do not have any relationships to disclose.

Pulmonary Vasculitides

Group of inflammatory disorders that are characterized by **damage/destruction of blood vessels**.

Low annual incidence (~100 new cases/million)

Presenting signs and symptoms can overlap with other clinical entities and lead to diagnostic delays.

These disorders and their treatment are associated with significant morbidity and mortality.

Pulmonary Vasculitides

CLASSIFICATION

CLINICAL PRESENTATION

DIAGNOSTIC TESTING

SPECIFIC DISORDER DESCRIPTIONS

TREATMENT

Pulmonary Vasculitides

- **Classification**
  - Primary
  - Secondary

Primary Pulmonary Vasculitides

- **Small**
  - Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV)
  - Idiopathic pauci-immune pulmonary capillaritis
- **Medium**
  - Polyarteritis nodosa
  - Kawasaki disease
- **Large**
  - Giant cell arteritis
  - Takayasu arteritis
- **Immune complex-mediated**
  - Anti-glomerular basement membrane (GBM) disease

  (formerly known as Goodpasture's syndrome)
  - IgA vasculitis

  (formerly known as Henoch-Schönlein purpura)

Primary Pulmonary Vasculitides

- **Small**
  - **Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV)**
  - **Idiopathic pauci-immune pulmonary capillaritis**
- **Medium**
  - Polyarteritis nodosa
  - Kawasaki disease
- **Large**
  - Giant cell arteritis
  - Takayasu arteritis
- **Immune complex-mediated**
  - Anti-glomerular basement membrane (GBM) disease (formerly known as Goodpasture's syndrome)
  - IgA vasculitis (formerly known as Henoch-Schönlein purpura)

Primary Pulmonary Vasculitides

- **Small**
  - Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV)
  - Idiopathic pauci-immune pulmonary capillaritis
- **Medium**
  - **Polyarteritis nodosa**
  - **Kawasaki disease**
- **Large**
  - Giant cell arteritis
  - Takayasu arteritis
- **Immune complex-mediated**
  - Anti-glomerular basement membrane (GBM) disease (formerly known as Goodpasture's syndrome)
  - IgA vasculitis (formerly known as Henoch-Schönlein purpura)

Primary Pulmonary Vasculitides

- **Small**
  - Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV)
  - Idiopathic pauci-immune pulmonary capillaritis
- **Medium**
  - Polyarteritis nodosa
  - Kawasaki disease
- **Large**
  - **Giant cell arteritis**
  - **Takayasu arteritis**
- **Immune complex-mediated**
  - Anti-glomerular basement membrane (GBM) disease (formerly known as Goodpasture's syndrome)
  - IgA vasculitis (formerly known as Henoch-Schönlein purpura)

Primary Pulmonary Vasculitides

- **Small**
  - Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV)
  - Idiopathic pauci-immune pulmonary capillaritis
- **Medium**
  - Polyarteritis nodosa
  - Kawasaki disease
- **Large**
  - Giant cell arteritis
  - Takayasu arteritis

- **Immune complex-mediated**
  - **Anti-glomerular basement membrane (GBM) disease**

    (formerly known as Goodpasture's syndrome)
  - **IgA vasculitis**

    (formerly known as Henoch-Schönlein purpura)

Secondary and other Pulmonary Vasculitides

- **Vasculitis associated with systemic disease**
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Scleroderma
  - Polymyositis/dermatomyositis
  - Anti-phospholipid antibody syndrome
  - Inflammatory bowel disease
- **Infection**
- **Cryoglobulinemic vasculitis**
- **Drug** (e.g., propylthiouracil, diphenylhydantoin)
- **Variable vessel vasculitis**
  - Behçet's disease
- **VEXAS syndrome**
  - Adult-onset inflammatory syndrome caused by myeloid lineage-restricted somatic mutations in UBA1

- **Malignancy**

Primary Pulmonary Small Vessel Vasculitides

- **Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV)**
  - Granulomatosis with polyangiitis (GPA)
    - Formerly known as Wegener's granulomatosis
  - Microscopic polyangiitis (MPA)
  - Eosinophilic granulomatosis with polyangiitis (EGPA)
    - Formerly known as Churg-Strauss syndrome

- **Idiopathic pauci-immune pulmonary capillaritis**

Pulmonary Vasculitides

Clinical Presentation

Pulmonary Vasculitides
Clinical Presentation

Hemoptysis/diffuse alveolar hemorrhage

Cavitary/nodular lung disease

Constitutional symptoms (fever, weight loss, malaise, arthralgias)

Extrapulmonary symptoms (upper airway, cutaneous and neurologic)

Pulmonary Nodules/Cavitary Lesions

Need to rule out infection and malignancy

Pulmonary nodules are a common presentation for granulomatosis with polyangiitis (GPA).

Vasculitis should be considered in patients with unexplained nodular or cavitary lung disease.

Rapidly Progressive Glomerulonephritis

Characterized by elevated blood urea nitrogen and serum creatinine and active urine sediment (proteinuria, hematuria and red cell casts).

Pulmonary-renal syndrome- combination of DAH + glomerulonephritis

Vasculitis should be considered in the setting of destructive upper or lower airway lesions and renal insufficiency.

Pulmonary Vasculitides

Laboratory and ANCA testing

Laboratory Testing

CBC and differential
Renal and liver function studies, urinalysis and sediment analysis
ANA, RF, anti-phospholipid antibody titers, anti-dsDNA, SS-A (Ro), SS-B (La), RNP and Jo-1 antibodies
Anti-glomerular basement membrane (GBM) antibodies
Immunoglobulin E if eosinophilic granulomatosis with polyangiitis (EGPA) is suspected
Pulmonary function testing

ANCA autoantibodies

Two main autoantigens in ANCA-associated vasculitis are:

Proteinase 3 (PR3)-serine proteinase present in neutrophils

Myeloperoxidase (MPO)- haem peroxidase enzyme present in neutrophils and monocytes that generates reactive oxygen species in anti-microbial defense.

Cornec, D. et al., *Nat Rev Rheum*, 12:570-579, 2016.

ANCA antibody testing

- **Enzyme-linked immunoabsorbent assay (ELISA)**
  - Immunoassays for proteinase 3 (Pr3) and myeloperoxidase (MPO) antibodies
- **Indirect immunofluorescence**
  - **cytoplasmic pattern (c-ANCA)**
    - antigen is usually proteinase 3 (Pr3)
  - **perinuclear pattern (p-ANCA)**
    - antigen is usually myeloperoxidase (MPO)
  - **atypical ANCA pattern**
- Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis" recommends **immunoassays for PR3 and MPO as the preferred screening method for AAV.**

Bossuyt, X. et al., *Nat Rev Rheum*, 13: 683-692, 2017.

Limitations of ANCA testing

ANCA positivity is NOT present in all forms of vasculitis and may be negative in patients with more limited disease.

A negative ANCA **does not** rule out vasculitis.

Positive ANCA, especially MPO-ANCA, can be seen in other inflammatory conditions such as rheumatoid arthritis, ulcerative colitis and other autoimmune disorders.

Bronchoscopy/Tissue Biopsy

Bronchoscopy is instrumental in assessing for infection and in the diagnosis of diffuse alveolar hemorrhage (DAH).

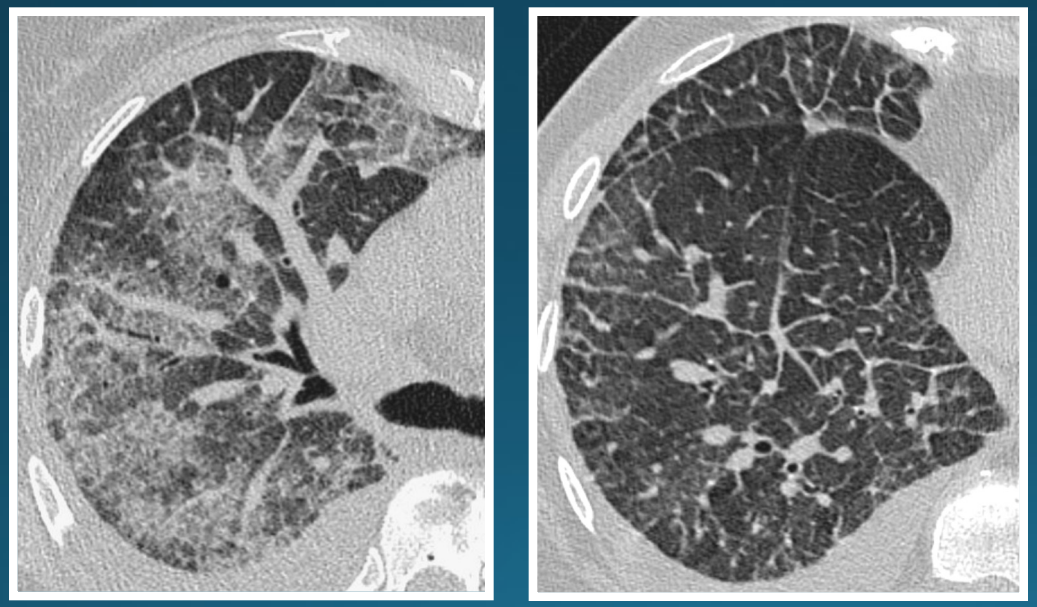
Transbronchial or endobronchial biopsies are unlikely to provide a tissue diagnosis of vasculitis but can provide supportive evidence in certain clinical presentations.

There are settings where a confident diagnosis can be made without a diagnostic biopsy (i.e. DAH and elevated MPO-ANCA or PR3-ANCA). However, tissue biopsy may be required. Renal, skin or sinus biopsies may confirm diagnosis and are associated with less morbidity than lung biopsy.

Transbronchial and surgical biopsies should be avoided in setting of DAH and respiratory failure due to high morbidity/mortality.

Diffuse Alveolar Hemorrhage (DAH)

- Often accompanied by hemoptysis and drop in hemoglobin.
- Should be suspected in patients with unexplained diffuse alveolar infiltrates on imaging.
- Hemoptysis is **not present** in up to 1/3 patients.
- Can be severe and life threatening.



before Rx

after Rx

Diffuse Alveolar Hemorrhage
Diagnosis

Usually diagnosed by increasingly bloody return in serial bronchoalveolar lavage (BAL) aliquots.

Diagnosis is also suggested by diffusion capacity >30% above baseline.

Pulmonary vasculitides accompanied by DAH usually have evidence of capillaritis on lung biopsy.

Diagnosis

- Diagnosis of vasculitis needs to be made based on comprehensive assessment of **clinical presentation, radiographic findings, serologic studies and tissue pathology.**

The Primary Small Vessel Pulmonary Vasculitides

Granulomatosis with polyangiitis (GPA)

(formerly known as Wegener's granulomatosis)

Granulomatosis with polyangiitis (GPA)

Most common ANCA-associated vasculitis.

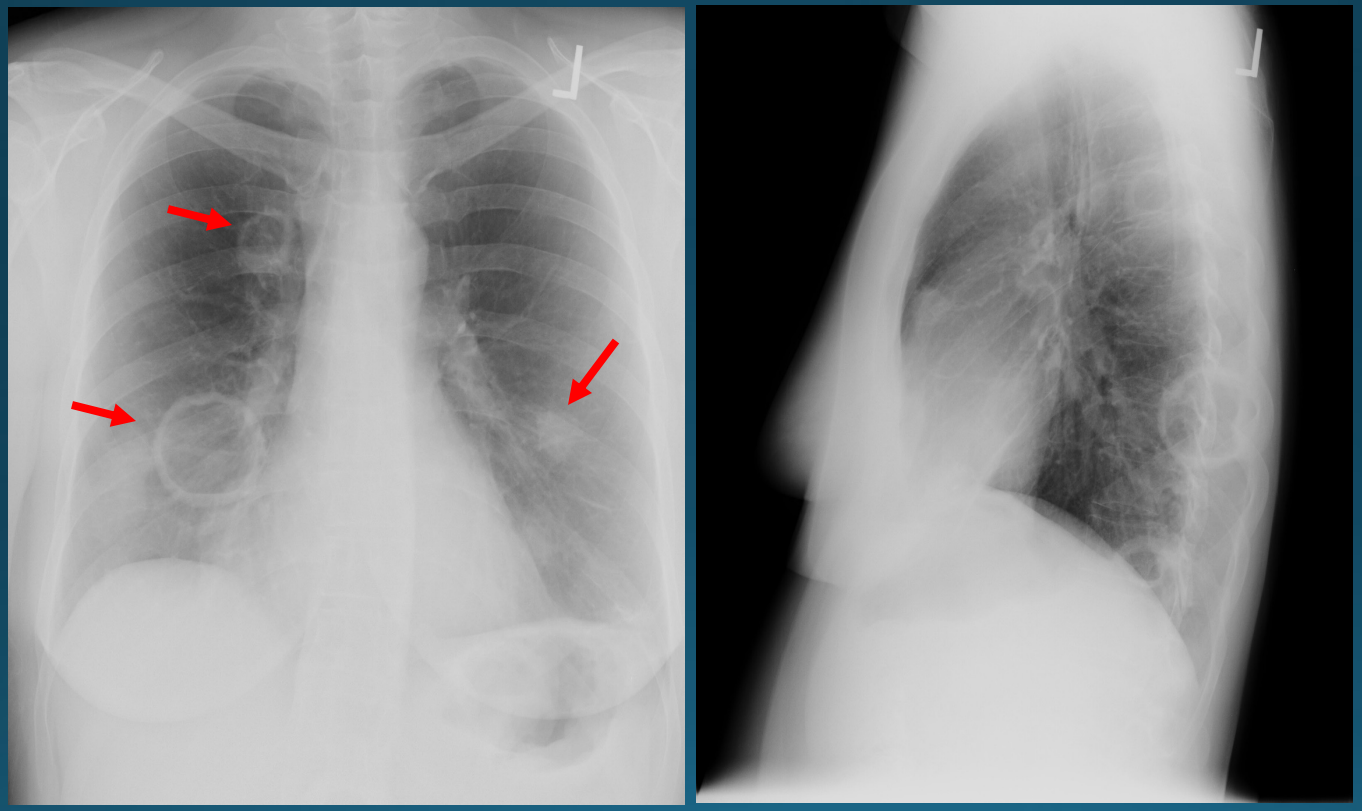
Although upper and lower respiratory tract disease and renal involvement is characteristic, all features are often not present at the time presentation.

High degree of renal involvement (40-90%).

Granulomatosis with polyangiitis (GPA)
Radiographic findings

Pulmonary nodules	**Occur in 40-70%**
	Cavitation is present in 50%
	Nodules may wax and wane
	Size 1-10 cm
Airspace disease	Diffuse alveolar hemorrhage
	Reticulonodular and interstitial infiltrates
	Consolidation
Airway disease	Subglottic stenosis
	Endobronchial lesions
	Bronchial stenosis

Granulomatosis with polyangiitis (GPA)



Cavitary and non-cavitary pulmonary nodules

Granulomatosis with polyangiitis (GPA)
Extrapulmonary manifestations

Renal disease	
Sinus disease	Epistaxis Destructive soft tissue/bone lesions Otitis
Ocular	Uveitis Episcleritis Scleritis Conjunctivitis
Musculoskeletal	Arthritis Arthralgias
Skin	Palpable purpura Nodules Ulcers

Granulomatosis with polyangiitis (GPA)
ANCA testing

- **85-95% positive** for PR3- (~75%) or MPO- (~20%) ANCA
- ANCA-negative disease is more often seen in patients with limited disease.
- Relationship of ANCA-titers to disease activity is not strong, although there may be specific scenarios where following titers may be useful.
- 2021 American College of Rheumatology/Vasculitis Foundation Guideline for Management of AAV recommends "against dosing immunosuppressive therapy based on ANCA titer results alone" in patients with GPA or MPA.

Almaani, S et al, *Journal of Clinical Medicine* (2021) 10: 1446
Chung, SA et al, *Arthritis Care and Research* (2021) 73: 1088-1105.

Granulomatosis with polyangiitis (GPA)

Pathology:

Necrotizing vasculitis of small and medium vessels with granulomatous inflammation and parenchymal necrosis.

Microscopic Polyangiitis (MPA)

Microscopic Polyangiitis (MPA)

Closely associated with rapidly progressive glomerulonephritis (RPGN). >90% patients have renal involvement.

Pulmonary involvement is observed in 30% at the time of presentation.

Capillaritis with DAH is most common pulmonary presentation.

Extrapulmonary findings include joint, skin, gastrointestinal and nervous system.

Almaani, S et al, *Journal of Clinical Medicine* (2021) 10: 1446

Microscopic Polyangiitis

- ANCA testing:
  - 67-96% positive for PR3- (~25%) or MPO- (60%) ANCA
  - p-ANCA is positive in 50-75%
  - c-ANCA is positive in 10-15%

- Pathology: Focal, segmental necrotizing vasculitis and mixed inflammatory infiltrate **without** granulomata.

Almaani, S et al, *Journal of Clinical Medicine* (2021) 10: 1446

Eosinophilic granulomatosis with polyangiitis (EGPA)

(formerly known as Churg-Strauss syndrome)

- Triad of asthma, hypereosinophilia and necrotizing vasculitis.
- Will be reviewed in detail in the Eosinophilic Lung Disease.

The Primary Small Vessel Pulmonary Vasculitides

Treatment

Randomized controlled trials (RCT) in ANCA-associated vasculitis

RAVE trial

- Rituximab in ANCA-associated Vasculitis (RAVE) trial
- Rituximab is an anti-CD20 monoclonal antibody that depletes B lymphocytes.
- Multicenter, randomized double-blind, noninferiority trial comparing rituximab + corticosteroids with cyclophosphamide + glucocorticoids for the induction of remission of severe ANCA-associated vasculitis.
- Excluded patients with respiratory failure and advanced renal disease (Cr > 4.0 mg/dl).
- Rituximab was not inferior to cyclophosphamide in the induction of remission in severe $ANCA^+$ vasculitis.

NEJM, 2010, 363 (3): 221-232.

Maintenance of remission: MAINRITSAN trial

- Compared a fixed, low-dose of rituximab to tapering dose of azathioprine for remission maintenance after induction with pulsed cyclophosphamide in AAV.

- At month 28, 29% of patients with AAV in azathioprine group had a major relapse vs 5% of patients treated with low-dose rituximab.

Guillevin, L. et al., *NEJM*, 371: 1771-80, 2014.

PEXIVAS

The Effects of Plasma Exchange and Reduced-Dose Glucocorticoids during Remission-Induction for Treatment of Severe ANCA-Associated Vasculitis

- Largest AAV study (704 patients)
- 2-by-2 factorial design
- Patients with severe AAV were randomized to induction therapy with cyclophosphamide or rituximab and IV methylprednisolone +/- plasma exchange.
- Patients were also randomly assigned to either a standard weight-based oral glucocorticoid regimen or a reduced-dose regimen (<60% of the standard regimen by 6 months).

Walsh, M. et al. *NEJM* 2020, 382: 622-631

PEXIVAS

The Effects of Plasma Exchange and Reduced-Dose Glucocorticoids during Remission-Induction for Treatment of Severe ANCA-Associated Vasculitis

- Primary composite outcome was death from any cause or end-stage renal disease. Patients were followed for up to 7 years.
- Plasma exchange **did not** reduce the risk of end-stage renal disease or death in patients with AAV.
- The primary outcome occurred in 28% of patients in the **reduced glucocorticoid group** and 26% in the standard glucocorticoid group and **met non-inferiority hypothesis**.
- Serious infections in the first year occurred **less often** in the reduced glucocorticoid group compared to the standard group (**incidence rate ratio 0.70**, p=0.02).

Walsh, M. et al. *NEJM* 2020, 382: 622-631

Avacopan for the treatment of ANCA-associated vasculitis
ADVOCATE

- Compared the C5a inhibitor avacopan vs oral prednisone on tapering schedule for remission induction in AAV
- All patients received either cyclophosphamide or rituximab followed by azathioprine for maintenance.
- Avacopan was non-inferior but not superior to prednisone taper to achieve remission at week 26.
- Avacopan was superior to prednisone taper for sustained remission at week 52.
- **Patients with severe DAH were excluded.**
- Avacopan is now FDA approved for use in AAV.

Jayne, D.R.W. et al. *NEJM 2021*, 384: 599-609

AAV Disease Categories

Category	Definition
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to GPA, MPA, or EGPA and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia)
Non-severe disease	Vasculitis without life- or organ-threatening manifestations
Remission	Absence of clinical signs or symptoms attributed to GPA, MPA, or EGPA, on or off immunosuppressive therapy
Refractory disease	Persistent active disease despite an appropriate course of immunosuppressive therapy
Relapse	Recurrence of active disease following a period of remission

American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophilic Cytoplasmic Antibody-Associated Vasculitis. Chung, SA et al., *Arthritis Care and Research*, 73:1088-1105, 2021.

Treatment options active, severe GPA/MPA

Recommended **remission induction** regimens:

Rituximab favored over cyclophosphamide

+ Reduced dose glucocorticoids over standard dose (after initial methylprednisolone pulse/high-dose oral glucocorticoids)

Remission induction **successful**

Remission induction **not** achieved

Recommended **remission maintenance** regimens (by order of preference):

1. **Rituximab**
2. **Methotrexate or azathioprine**
3. **Mycophenolate or leflunomide**

Recommended **switching** to a different remission induction agent (rituximab or cyclophosphamide) over combining remission induction agents

Adapted from 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophilic Cytoplasmic Antibody-Associated Vasculitis. Chung, SA et al., *Arthritis Care and Research*, 73:1088-1105, 2021.

Treatment options active, non-severe GPA

Recommended **remission induction** regimens:

Methotrexate + glucocorticoids favored over:

Rituximab + glucocorticoids

Cyclophosphamide + glucocorticoids

Azathioprine + glucocorticoids

Mycophenolate + glucocorticoids

Glucocorticoids

Remission induction **successful**

Remission induction **not** achieved

Remission on methotrexate, azathioprine or mycophenolate: continue same regimen for maintenance.

Remission on rituximab or cyclophosphamide: consider rituximab, methotrexate, azathioprine or leflunomide for maintenance.

Recommended **switching** to a different remission induction agent (options as noted above)

Adapted from 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophilic Cytoplasmic Antibody-Associated Vasculitis. Chung, SA et al., *Arthritis Care and Research*, 73:1088-1105, 2021.

Additional treatment recommendations from 2021 AAV guidelines

- Addition of plasma exchange to remission induction therapy is **not recommended** in patients with active, severe GPA/MPA with alveolar hemorrhage
  - It is recommended if patients also have anti-GBM disease
  - May be considered in patients who have active glomerulonephritis at high risk for progression to ESRD, are critically ill, or who are not responding to remission induction therapies.
- Dosing immunosuppressive therapy based on ANCA titers alone is **not recommended**
- For patients receiving rituximab for GPA/MPA maintenance, **scheduled re-dosing** is recommended over the use of ANCA titers or CD19+ B cell counts
- For patients with rituximab-associated hypogammaglobulinemia and recurrent severe infections, immunoglobulin supplementation is recommended
- For patients with GPA and actively inflamed subglottic and/or endobronchial tissue with stenosis, **treatment with immunosuppressive therapy is recommended** over surgical dilation with intralesional glucocorticoid injection alone
  - Surgical dilation with intralesional injection may be appropriate for stenoses that are longstanding, fibrotic or unresponsive to immunosuppression and may also be considered as initial therapy for stenosis that require immediate intervention such as for critical narrowing.

American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophilic Cytoplasmic Antibody-Associated Vasculitis. Chung, SA et al., *Arthritis Care and Research*, 73:1088-1105, 2021.

Additional considerations

- Prophylaxis
  - *Pneumocystis jirovecii*, osteoporosis, vaccinations
- Drug toxicity
  - Cyclophosphamide
  - Methotrexate
  - Corticosteroids
  - Rituximab
- Thromboembolic disease

Summary

- The primary pulmonary small vessel vasculitides are a group of inflammatory disorders that **damage/destroy blood vessels** and may be associated with extrapulmonary manifestations.
- There is significant morbidity/mortality associated with their treatment.
- Patients that present with DAH, pulmonary nodules with or without cavitation and acute renal failure should be evaluated for pulmonary vasculitis.
- ANCA testing and **screening for secondary pulmonary vasculitis disorders and infection** should be performed on all patients with suspected vasculitis.
- ANCA testing for **PR3-ANCA and MPO-ANCA antibodies** is the preferred method for screening for ANCA-associated vasculitis.
- ANCA antibody specificity is important in predicting response to therapy, prognosis and clinical phenotyping.
- There are new (2021) guidelines for categorization of ANCA-associated vasculitis disease severity and treatment.

References

- Collard, H.R. and Schwarz, M.I. Diffuse alveolar hemorrhage. (2004) *Clin. Chest Med.* 25:583-592.
- Frankel, S. K. and D. Jayne. The Pulmonary Vasculitides. (2010) *Clin. Chest Med.* 31:519-536.
- Jennette, J.C. et. al. Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (2013) *Arthritis and Rheumatism* 65:1-11.
- Bossuyt, X. et. al. Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis (2017) *Nat Rev Rheum* 13:683-692.
- Cartin-Ceba, R. et. al. Diffuse alveolar hemorrhage secondary to antineutrophil cytoplasmic antibody-associated vasculitis: predictors of respiratory failure and clinical outcomes (2016) *Arthritis Rheumatol* 68: 1467-1476.
- Unizony, S. et. al. Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type (2016) *Ann Rheum Dis* 75:1166-1169.
- Walsh, M. et. al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis (2020) *NEJM*, 382: 622-631.
- Chung, S.A. et al. American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophilic Cytoplasmic Antibody-Associated Vasculitis (2021) *Arthritis Care and Research*, 73:1088-1105, 2021.

Review Question

1.

- A 37-year-old computer engineer with a history of hypertension and hypercholesterolemia is referred for evaluation of dyspnea and acute renal insufficiency.

- He denies sputum production, fevers, or productive cough. He notes that he wheezes intermittently and was recently started on empiric treatment with inhaled corticosteroids by his primary care physician.

- He has had left ear pain and episodic epistaxis. His flow volume tracings demonstrate flattening of the inspiratory loop.

- His PR3 antibody titer is significantly elevated and renal biopsy demonstrates necrotizing crescentic glomerulonephritis.

What treatment should your multidisciplinary team recommend?

A. Methotrexate with reduced dose corticosteroids
B. Cyclophosphamide with reduced dose corticosteroids
C. Rituximab with standard dose corticosteroids
D. Rituximab with reduced dose corticosteroids

What treatment should your multidisciplinary team recommend?

A. Methotrexate with reduced dose corticosteroids
B. Cyclophosphamide with reduced dose corticosteroids
C. Rituximab with standard dose corticosteroids
D. Rituximab with reduced dose corticosteroids

Question 1. Brief justification

- The patient has an elevated PR3 ANCA antibody titer, acute renal insufficiency, symptoms concerning for sinus (epistaxis) and airway involvement (flattening of flow volume loop), and renal biopsy that demonstrated necrotizing crescentic glomerulonephritis, which is consistent with the diagnosis of GPA.
- The new 2021 American College of Rheumatology/Vasculitis Foundation guidelines recommend rituximab + glucocorticoids as first line treatment for active, severe GPA/MPA. Acute glomerulonephritis is considered organ-threatening severe disease.
- Methotrexate + glucocorticoids is the recommended first line treatment combination for active, non-severe GPA.
- The PEXIVAS study demonstrated that reduced-dose corticosteroid regimen (after methylprednisolone pulse/high-dose oral glucocorticoids) resulted in similar outcomes and decreased risk of infection.

Conflict of Interest/Affiliation Disclosure Statement

I do not have any relationships to disclose.