# ANCA-Associated Vasculitis: Core Curriculum 2020

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of disorders characterized by inflammation and destruction of small- and medium-sized blood vessels and the presence of circulating ANCA. Clinical disease phenotypes include granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, and renal-limited vasculitis. Serologic classification of AAV into proteinase 3–ANCA disease and myeloperoxidase-ANCA disease correlates with a number of disease characteristics. AAV has a predilection for the kidney, with >75% of patients having renal involvement characterized by rapidly progressive glomerulonephritis. The cause and pathogenesis of AAV are multifactorial and influenced by genetics, environmental factors, and responses of the innate and adaptive immune system. Randomized controlled trials in the past 2 decades have refined the therapy of AAV and transformed AAV from a fatal disease to a chronic illness with relapsing course and associated morbidity. This article in *AJKD*'s Core Curriculum in Nephrology series provides a detailed review of the epidemiology, pathogenesis, diagnosis, and advances in the management of AAV.

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## Classification of Vasculitis

The most widely used classification system for systemic vasculitis is that defined at the 2012 International Chapel Hill Consensus Conference (CHCC), which stratifies vasculitis according to vessel size (Box 1). Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is divided into 3 clinical diseases (granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA], and eosinophilic GPA [EGPA]). Each of these conditions is commonly associated with a circulating ANCA, with the major target antigens identified as proteinase 3 (PR3) and myeloperoxidase (MPO).

One of the current controversial issues in AAV is the definition of disease based on clinical phenotype (GPA vs MPA) because there is significant overlap in clinical features between these 2 diseases. It has been suggested that AAV should be classified according to ANCA specificity (PR3-ANCA disease vs MPO-ANCA disease). Relapse rates (higher in PR3-ANCA) and clinical outcomes (mortality higher in MPO-ANCA) associate better with ANCA specificity, and genetic studies segregate more closely with ANCA specificity than clinical phenotype. The CHCC 2012 advocated for adding a prefix to the clinical phenotype in a given patient with AAV (eg, PR3-ANCA GPA or MPO-ANCA GPA). A large multinational study (>6,000 patients from 136 sites in 32 countries), the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), is currently collecting data to develop new diagnostic criteria and update the classification for systemic vasculitis.

## Epidemiology of AAV

AAV is an uncommon disease with an incidence of about 20 per million population per year in Europe and North America. There is a slight male preponderance. Incidence increases with age, with a peak in the 60- to 70-year age range. AAV is more common in white and Asian populations and less common in African American populations. There is notable geographic variation, with GPA being more common in Northern Europe and Australia/New Zealand, whereas MPA is more common in Southern Europe and Asia. It is unclear whether this represents genetic differences or other environmental factors such as vitamin D levels and sun exposure.

Infection with *Staphylococcus aureus* may trigger episodes of AAV; notably, GPA is more common in winter months, and chronic nasal carriage of *S aureus* has been associated with an increased risk for disease relapse. Furthermore, a double-blind placebo-controlled trial of trimethoprim in patients with GPA reported fewer respiratory tract infections and a significantly lower relapse rate. Other environmental factors include silica exposure, hydrocarbon exposure, and pesticides and medications (see Drug-Induced Vasculitis).

## Genetics

Familial forms of AAV have been described but are rare. Two genome-wide association



*The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.*

**Box 1.** Systemic Vasculitis Nomenclature

**Small-vessel vasculitis (SVV)**
- Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
  - ◇ Microscopic polyangiitis (MPA)
  - ◇ Granulomatosis with polyangiitis (Wegener) (GPA)
  - ◇ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
- Immune complex SVV
  - ◇ Anti–glomerular basement membrane (anti-GBM) disease
  - ◇ Cryoglobulinemic vasculitis (CV)
  - ◇ Immunoglobulin A (IgA) vasculitis (Henoch-Schönlein) (IgAV)
  - ◇ Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

**Medium-vessel vasculitis (MVV)**
- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

**Large-vessel vasculitis**
- Takayasu arteritis (TA)
- Giant cell arteritis (GCA)

**Variable vessel vasculitis (VVV)**
- Behçet disease (BD)
- Cogan syndrome (CS)

Based on 2012 International Chapel Hill Consensus Conference (see Jennette et al in Additional Readings).

studies in European and North American populations have identified disease susceptibility loci in AAV. GPA is associated with single-nucleotide polymorphisms in *HLA-DP*, *PRTN3* (encoding PR3), and *SERPINA1* (encoding $\alpha_1$-antitrypsin, a protease acting as the major inhibitor of PR3). PR3-ANCA disease–associated variants in *PRTN3* and *SERPINA1* support the hypothesis that PR3-ANCA is not merely an epiphenomenon in AAV, but plays a central role in the pathogenesis of this disease. By contrast, MPA was associated with *HLA-DQ* polymorphisms. It is worth noting that the strength of these genetic associations was greater with respect to ANCA specificity (PR3-ANCA or MPO-ANCA) than for clinical phenotype (GPA or MPA).

## Additional Readings


- Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum.* 2013;65(1):1-11. ★ ESSENTIAL READING
- Lionaki S, Blyth ER, Hogan SL, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. *Arthritis Rheum.* 2012;64(10):3452-3462.
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- Unizony S, Villarreal M, Miloslavsky EM, et al. Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. *Ann Rheum Dis.* 2016;75(6):1166-1169.


## ANCA Antibodies

ANCAs are autoantibodies directed against cytoplasmic antigens expressed in the primary granules of neutrophils and the lysosomes of monocytes. Neutrophil primary granules contain a range of antibacterial proteins, including lysozyme, MPO, neutral serine proteinases (PR3, elastase, and cathepsin G), and acid hydrolases (cathepsin B and D). Autoantibodies may develop against any of these proteins, but the clinically relevant antibodies are directed against MPO and PR3. During the active stage of disease, ANCAs are typically immunoglobulin G (IgG), but other immunoglobulin classes (IgM and IgA) are described.

## ANCA Testing

Many laboratories use indirect immunofluorescence assay (IIF) as a screening test for ANCA. Although both MPO and PR3 are found in primary granules, 2 major immunostaining patterns are seen. Ethanol fixation leads to dissolution of primary granules, and the cationic MPO attaches to the negatively charged nuclear membrane giving a perinuclear pattern (pANCA), whereas PR3 remains distributed in a cytoplasmic pattern (cANCA). When a positive IIF result is identified, the target antigen is confirmed by an antigen-specific immunoassay (enzyme-linked immunosorbent assay). A 2017 international consensus statement on ANCA testing recommended initial testing for suspected AAV with immunoassays for PR3-ANCA and MPO-ANCA, rather than IIF.

## ANCA and Disease Associations

PR3-ANCA is most commonly associated with GPA (75%), whereas MPO-ANCA is more commonly associated with MPA (60%) or renal-limited vasculitis (80%; Table 1). Atypical ANCAs, which are not directed against either PR3 or MPO (positive IIF and negative enzyme-linked immunosorbent assay), can be found in a range of nonvasculitic conditions (inflammatory bowel disease, autoimmune disease, and malignancy). PR3-ANCA or MPO-ANCA may also be found in chronic infections (endocarditis, tuberculosis, human immunodeficiency virus [HIV], hepatitis C, and bartonellosis). The presence of both anti-MPO and anti-PR3 antibodies in the same patient is very rare and suggestive of drug-induced vasculitis.

## ANCA-Negative Pauci-Immune Vasculitis

A subgroup (~10%) of patients with clinical features and pathology consistent with AAV remain ANCA negative on testing. Although these patients may have a similar clinical course and response to treatment, ANCA-negative patients are more likely to have renal-limited disease or less severe systemic disease. In some of these ANCA-negative patients, epitope mapping by a highly sensitive epitope excision/mass spectrometry approach led to the discovery of a pathogenic MPO-ANCA that is reactive to a restricted epitope. The detection of this specific MPO-ANCA using

**Table 1.** Frequency of ANCA Positivity in Different Conditions

| | PR3-ANCA (mostly cANCA) | MPO-ANCA (mostly pANCA) | Other |
|---|---|---|---|
| **ANCA-Associated Vasculitis** | | | |
| GPA | 75% | 20% | 5% ANCA negative |
| MPA | 30% | 60% | 10% ANCA negative |
| EGPA | 5% | 45% | 50% ANCA negative |
| Renal-limited vasculitis | 10% | 80% | 10% ANCA negative |
| Drug-induced vasculitis | 10% | 90% | Often high titer, dual positivity for MPO and PR3 |
| **Nonvasculitis Conditions** | | | |
| Systemic lupus | 2% | 10% | 10% atypical ANCA |
| Endocarditis | 15% | 5% | |
| Inflammatory bowel disease | Negative | Negative | Atypical ANCA, various antigens: ulcerative colitis (50%-67%), Crohn disease (6%-15%) |
| Primary sclerosing cholangitis | Negative | Negative | Atypical ANCA, various antigens: 60%-80% |
| Cystic fibrosis | Negative | Negative | Atypical ANCA pattern, directed against BPI (90%) |

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; BPI, bactericidal/permeability-induced protein; cANCA, cytoplasmic antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; pANCA, perinuclear antineutrophil cytoplasmic antibody; PR3, proteinase 3.

standard assays is masked by ceruloplasmin, a natural inhibitor of MPO.

### Additional Readings


- Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Position paper: revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. *Nat Rev Rheumatol.* 2017;13(11):683-692.


## Pathophysiology

### Development of ANCAs

It is unclear why autoantibodies to neutrophil self-antigens develop because both MPO and PR3 are sequestered from the immune system in primary granules, and following neutrophil degranulation at sites of tissue injury, are rapidly eliminated by specific inhibitors ($\alpha_1$-antitrypsin [PR3] and ceruloplasmin [MPO]). Defective neutrophil apoptosis, or impaired clearance of apoptotic cell fragments, may lead to prolonged exposure of these antigens to the immune system. Infection may also play a role through molecular mimicry, in which antibodies to microbial antigens cross-react with neutrophil antigens, or possibly through the development of antibodies to complementary peptides and subsequent host immune response to these anti-complementary PR3 antibodies.

## Role of ANCAs

Experimental and clinical data provide evidence that ANCAs are not only biomarkers of AAV, but play an important role in pathogenesis. This was first demonstrated in a series of experiments using a passive transfer model of anti-MPO crescentic glomerulonephritis (GN). MPO-deficient mice immunized with mouse MPO produce high-titer anti-MPO antibodies, and when these antibodies were injected into wild-type mice, the animals developed crescentic GN and pulmonary hemorrhage. Notably, neutrophil depletion abrogated the disease in these mice, confirming the central role of neutrophils. In a second animal model, WKY rats immunized with human MPO developed MPO-ANCA and necrotizing renal and pulmonary vasculitis. A human case of transplacental transfer of anti-MPO antibodies from mother to fetus with subsequent neonatal pulmonary hemorrhage and GN has been described in a premature infant born at 33 weeks. Notably, attempts to develop an animal model for vasculitis caused by PR3-ANCA have not been successful. This has been attributed to differences in the biology of PR3-ANCA in humans and experimental animals.

### Neutrophil Priming and Activation

Neutrophils are the main mediators of vessel injury. In response to infection or inflammation, neutrophils exposed to inflammatory cytokines (tumor necrosis factor α and interleukin 1), lipopolysaccharide or complement C5a become primed with movement of MPO and PR3 from primary granules to the neutrophil surface. In this primed state, ANCAs may bind to these autoantigens on the cell surface, resulting in robust cellular activation. Activated neutrophils alter the expression of adhesion molecules and bind to vascular endothelium. Neutrophil degranulation results in the release of reactive oxygen species and proteases mediating tissue injury. Activated neutrophils also undergo a specific form of cell death (NETosis) in which neutrophil extracellular traps (NETs) are extruded from the cell containing entrapped MPO, PR3, and complement components in a chromatin web. NETs can mediate direct injury to endothelium, transfer MPO/PR3 to vascular endothelium and dendritic cells for

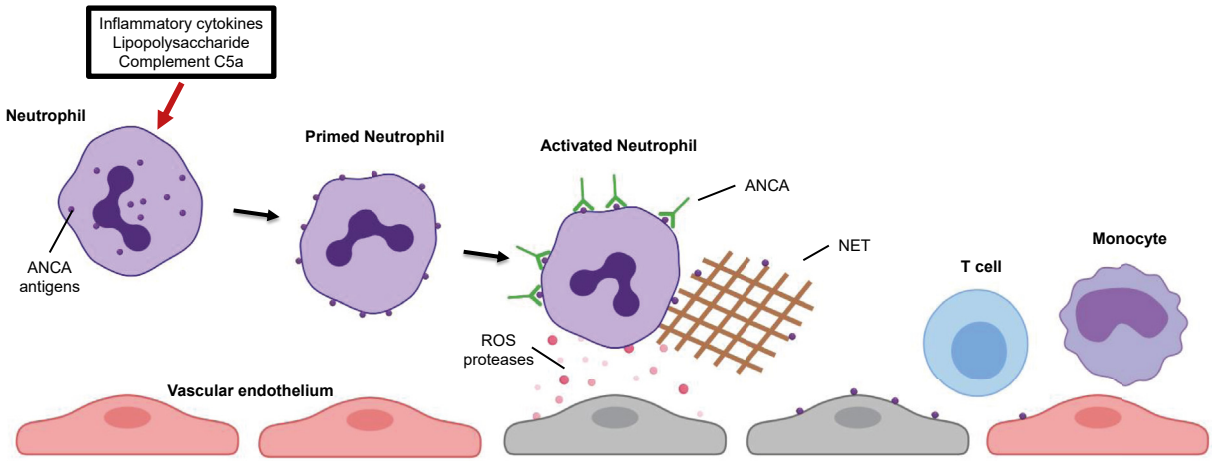


**Figure 1.** Pathogenesis of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. ANCA autoantigens (proteinase 3 [PR3] and myeloperoxidase [MPO]) are normally sequestered in the primary granules of neutrophils. Infection or other environmental stimuli result in neutrophil priming, with movement of PR3 and MPO to the cell surface. Binding of ANCA to these autoantigens results in activation of neutrophils, which adhere to vascular endothelium. Neutrophil degranulation leads to the release of reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs), damaging the endothelium. Chemokines and tissue deposition of PR3 and MPO result in the recruitment of autoreactive T cells and monocytes augmenting tissue injury. Drawings created with BioRender.

antigen presentation, and activate the alternate pathway of complement. Chemokines and tissue deposition of PR3 and MPO result in the recruitment of autoreactive T cells and monocytes augmenting tissue injury (Fig 1).

## Role of Complement

Historically it was considered that complement played a limited role in AAV due to the paucity of complement deposition seen on kidney biopsy and the absence of hypocomplementemia. Recent evidence from the anti-MPO model in a variety of complement-deficient mice has demonstrated a role for the alternate pathway of complement, and specifically, the anaphylatoxin C5a and C5a receptor (CD88) seems central to this process. An amplification loop has been proposed in which activated neutrophils release properdin, promoting the alternate pathway and generating the anaphylatoxin C5a, which binds to C5a receptors on neutrophils, leading to further neutrophil priming and activation (Fig 2).

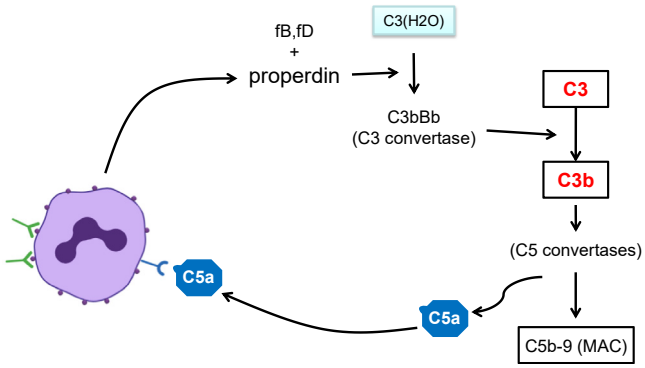


**Figure 2.** Role of complement in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. ANCA binding to autoantigens (proteinase 3 and myeloperoxidase) on the cell surface results in neutrophil activation and release of factors (properdin) that activate the alternate pathway of complement. The membrane attack complex (MAC; C5b-9) plays a limited role, but generation of the anaphylatoxin C5a attracts further neutrophils, and on binding to the cell surface C5a receptor (CD88) enhances neutrophil priming and activation, resulting in the formation of an amplification loop promoting inflammation. Neutrophil drawing created with BioRender.

Recent studies of humans support these findings, with the demonstration of alternate pathway activation in the circulation and tissue deposition of complement components of the alternate pathway more commonly recognized. Elevated circulating and urinary C5a levels have been described in active AAV, and low levels of circulating C3 (found in 5%-20% of patients) are associated with worse outcomes. Most excitingly, early clinical studies using the C5a receptor antagonist avacopan have supported an important role of C5a in AAV.

## Additional Readings


- Hutton HL, Holdsworth SR, Kitching AR. ANCA-associated vasculitis: pathogenesis, models, and preclinical testing. *Semin Nephrol.* 2017;37(5):418-435.
- Prendecki M, Pusey CD. Recent advances in understanding of the pathogenesis of ANCA-associated vasculitis. *F1000Res.* 2018;7;doi:10.12688/f1000research.14626.1.


## Kidney Pathology

The pathologic hallmark of ANCA-associated GN is necrotizing and/or crescentic GN without significant immune complex deposition that is detectable using

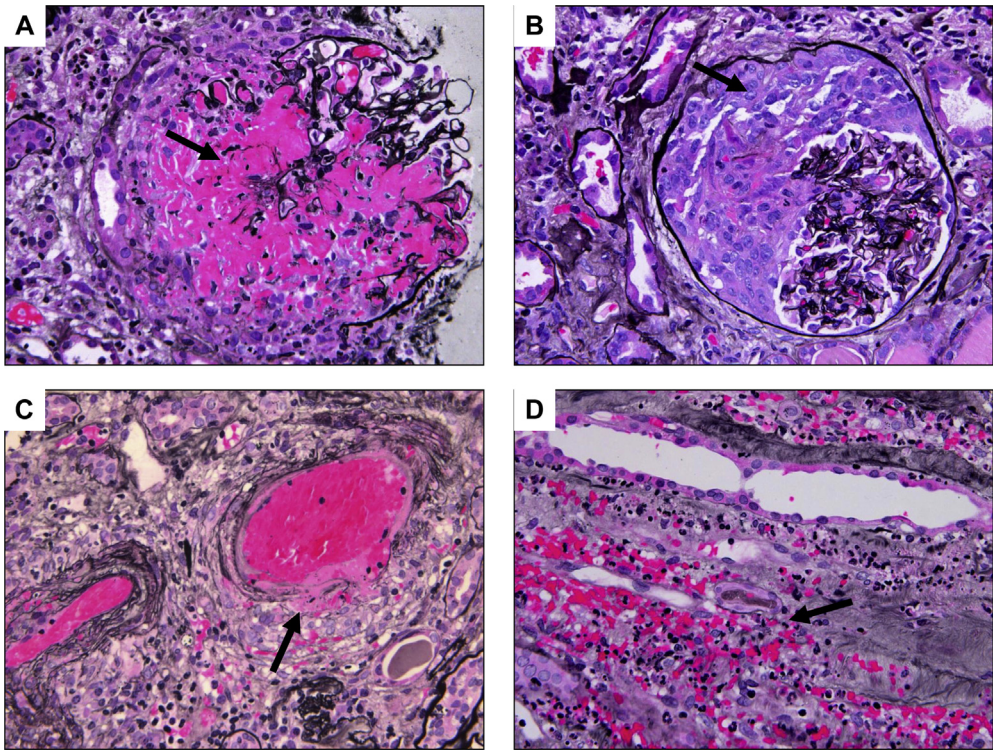


**Figure 3.** Kidney pathology. Light microscopy images (Jones methenamine silver stain) show typical features of a necrotizing crescentic glomerulonephritis: (A) glomerulus with segmental necrosis (arrow) and (B) large glomerular crescent (arrow) filling most of Bowman space and compressing the glomerular tuft. Less commonly seen is (C) necrotizing extraglomerular vasculitis (arrow), and rarely, (D) medullary angiitis (arrow) with prominent neutrophils. Images provided courtesy of Shreeram Akilesh.

immunofluorescence or electron microscopy. The areas of necrosis may be small and segmental or may be more extensive with large circumferential crescents (Fig 3A and B). Occasionally, these can rupture the Bowman capsule, provoking a brisk tubulointerstitial inflammatory response. If there is no other underlying kidney disease, the unaffected glomeruli and non-necrotic lesions in segmentally affected glomeruli look unremarkable. Less commonly, patients may show extraglomerular renal vasculitis (Fig 3C and D). Although pauci-immune, small amounts of IgG or C3 may be seen and if present, have been associated with more severe disease. Neutrophil-rich inflammation of medullary vessels (medullary angiitis) may also be seen, sometimes in isolation and in other instances concurrent with renal cortex involvement by GN and vasculitis (Fig 3D). In contrast to GPA and MPA, EGPA is characterized by prominent eosinophil-rich inflammation in granulomas surrounding necrotizing vasculitis of interlobular-sized and larger vessels.

## Clinical Features

***Case 1:*** *A 60-year-old woman with nasal crusting for 6 months presents with fever, migratory arthralgia, progressive fatigue, and a 20-lb weight loss over 3 months. Physical examination is notable for purpura in the lower extremities. Laboratory data are significant for increased levels of inflammatory markers, a subacute increase in serum creatinine (Scr) level from a baseline of 1.0 mg/dL to 2.2 mg/dL, and proteinuria and hematuria seen on urinalysis. Serologic tests are positive for PR3-ANCA at a titer of 63 U/mL. Antinuclear antibody is positive at 1:40, and serum C3 and C4 levels are normal. MPO-ANCA and anti–glomerular basement membrane (anti-GBM) are negative. Computed tomography (CT) of the chest reveals lung nodules. Skin biopsy reveals findings consistent with a leukocytoclastic vasculitis with absence of immune deposits on direct immunofluorescence. A kidney biopsy is performed.*

**Question 1: What is the most likely diagnosis?**

a) GPA
b) MPA
c) EGPA
d) Systemic lupus erythematosus

*For the answer to the question, see the following text.*

A typical presentation of GPA is characterized by constitutional symptoms, chronic sinusitis, arthralgia, leukocytoclastic skin rash, lung nodules, acute kidney injury from biopsy-proven necrotizing and crescentic pauci-immune GN, and PR3-ANCA positivity. The absence

**Table 2.** Comparison of Clinical Features by ANCA Specificity

| | PR3-ANCA | MPO-ANCA |
|---|---|---|
| Demographics | 50-70 y | 60-80 y (mean, 10 y older than PR3-ANCA) |
| Geography | Northern Europe, North America | Southern Europe, Asia |
| Genetic risk alleles | *HLA-DP, PRTN3, SERPINA1* | *HLA-DQ* |
| Pathology | Necrotizing vasculitis, granulomatous inflammation | Necrotizing vasculitis, no granulomatous inflammation |
| Renal | More acute presentation | More common, more chronic injury on biopsy, may have a slow indolent course, more likely renal limited, isolated interstitial kidney disease (rare), usually MPO-ANCA |
| Respiratory involvement | More common; nodules, cavitation, and central airway disease more specific to PR3 | Less common; may be chronic lung fibrosis, peripheral reticulation, honeycombing and usual interstitial pneumonia more specific to MPO |
| Upper airway disease | More common, destructive lesions (nasal perforation, saddle nose) | Rare |
| Outcomes | More likely to have resistant disease | Worse long-term survival (more chronic injury) |
| Relapse rate | Higher | Lower |
| Treatment | May respond better to rituximab than cyclophosphamide | Similar response to rituximab and cyclophosphamide |

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

of immune complex deposition in skin and kidney excludes lupus nephritis. Thus, the answer to question 1 is (a).

Although there is significant overlap in the clinical features of GPA and MPA, MPA is distinguished from GPA clinically by the lack of granulomatous manifestations and serologically by its more frequent association with MPO-ANCA type (Table 2). EGPA is similar to GPA in that it is characterized by granulomatous inflammation and necrotizing vasculitis involving small- and medium-sized vessels but is distinguished from GPA by the presence of eosinophilia and asthma. ANCA is positive in only ~50% of patients of EGPA, typically MPO-ANCA. Renal involvement occurs in 20% of patients with EGPA, but only the ANCA-positive group develops a necrotizing crescentic GN.

## Kidney Involvement in AAV

Kidney disease is common in AAV and is the most important predictor of mortality. Those who present with glomerular filtration rates (GFRs) < 50 mL/min have a 50% risk for death or kidney failure at 5 years. The typical renal presentation is that of a rapidly progressive GN with a decline in kidney function accompanied by sub–nephrotic-range proteinuria, microscopic hematuria, and hypertension over days to a few months. Kidney biopsy typically reveals a pauci-immune focal necrotizing crescentic GN. In patients with MPO-ANCA, a more long-term presentation may be found, with features of irreversible kidney injury (glomerulosclerosis and interstitial fibrosis) and poor response to immunosuppression. Although the necrotizing crescentic GN is typically pauci-immune, evidence of immune complex deposition is found in >50% of biopsies and is associated with higher levels of proteinuria and higher percentage of glomerular crescents. Rarely, interstitial nephritis in the absence of glomerular involvement may be found secondary to vasculitis of the vasa recta. Granulomatous inflammation presenting as a renal mass is a rare presentation in GPA.

Timely initiation of therapy is critical to prevent kidney progression to kidney failure regardless of GFR at presentation. Remission of kidney disease is defined as stabilization or improvement in Scr level and resolution of hematuria. Proteinuria can be present during remission, reflecting structural damage from vasculitis. Age, MPO-ANCA, low GFR at entry, lower percentage of normal glomeruli, and higher degree of tubular atrophy are all correlated with poor outcomes. Relapse of renal vasculitis is another important predictor of kidney failure and in the absence of a reliable biomarker for renal relapse, close monitoring for an increase in Scr level and recurrence of hematuria remains an integral component of long-term management of patients with AAV.

However, the value of ANCA monitoring in predicting relapse is controversial. In patients with renal involvement at baseline, ANCA level increase during serial monitoring has been demonstrated to predict relapse. Given the pathogenic role of macrophages and T cells, urinary biomarkers of activation of these cells may predict disease activity. Levels of macrophage-derived urinary soluble CD163 and serum and urinary CD25 have recently been shown to predict renal relapse.

## Systemic Features of AAV

Constitutional symptoms (fatigue, myalgia, and fevers) are prominent and may be present for several months before presentation. The lungs are more commonly involved in GPA, and pulmonary necrotizing granulomatous lesions may produce cavitation or nodular lesions seen on CT. Upper respiratory tract disease may present as rhinitis, sinusitis, otitis media, or granulomatous inflammation leading to septal perforation and nasal collapse. Upper respiratory tract involvement is less common in MPA and

lung involvement in MPA typically presents as alveolar hemorrhage and may be associated with pulmonary fibrosis. Hearing loss or scleritis/uveitis may occur. A purpuric rash on the lower extremities is common, secondary to a leukocytoclastic vasculitis. Cutaneous nodular lesions may be seen in GPA. Peripheral neuropathy, typically mononeuritis multiplex, occurs but central nervous system involvement is rare. Mesenteric vasculitis may present with abdominal pain and blood in the stool. Rarely, vasculitis in liver or pancreas can mimic hepatitis or pancreatitis. Cardiac involvement with myocarditis or heart block is rare. Venous thrombosis can occur in the active phase of vasculitis and may be associated with antiplasminogen antibodies.

## Other Variant Forms of AAV

### Drug-Induced Vasculitis

A number of therapeutic agents are associated with small-vessel vasculitis, including hydralazine, propylthiouracil, minocycline, and anti–tumor necrosis factor agents. Drug-induced vasculitis is often characterized by high-titer MPO-ANCA and the presence of other autoantibodies such as antinuclear antibodies. Hydralazine-associated vasculitis can be severe, with predilection for the kidney. Cocaine adulterated with levamisole causes a distinct type of ANCA vasculitis characterized clinically by prominent necrotic skin lesions in addition to vasculitic involvement of major organs and serologically by dual positivity for PR3-ANCA and MPO-ANCA.

### Dual-Positive ANCA and Anti-GBM Disease

A subset of patients with crescentic GN have dual-positive disease characterized by the presence of both ANCAs and anti-GBM antibody. Copresentation of ANCA and anti-GBM antibody occurs at a higher frequency than anticipated by chance alone. About 10% to 40% of patients with anti-GBM disease test positive for ANCA, almost exclusively to MPO, and 5% to 14% of patients with AAV have circulating anti-GBM antibody. The mechanism of this association is speculative, although it has been shown that ANCAs may be detected first and the glomerular inflammation induced by ANCAs could expose sequestered epitopes in the GBM, triggering anti-GBM antibodies. Clinically, these patients have severe disease at presentation with early morbidity and mortality similar to patients with anti-GBM, while their long-term course is characterized by disease relapses similar to patients with AAV.

## Induction Therapy

***Case 2:*** *A 48-year-old woman with a history of PR3-ANCA GN at age 45 years presents to the emergency department with progressive fatigue, night sweats, and fever for 2 months, and 3 days of worsening dyspnea and hemoptysis. Her laboratory data are notable for increased erythrocyte sedimentation rate, C-reactive protein level, and acute kidney injury (Scr of 3.5 mg/dL); urinalysis shows proteinuria and hematuria. PR3-ANCA is positive at a titer of 190 U/mL. Anti-GBM is negative. CT of the chest shows bilateral ground glass infiltrates and kidney biopsy reveals a pauci-immune GN.*

**Question 2: What is the preferred treatment regimen for this patient?**

a) Pulse methylprednisolone followed by oral prednisone
b) Cyclophosphamide and glucocorticoids
c) Rituximab and glucocorticoids
d) Plasmapheresis, cyclophosphamide, and glucocorticoids

*For the answer to the question, see the following text.*

This patient presents with a typical case of severe PR3-ANCA relapsing vasculitis with pulmonary and renal involvement. Treatment of AAV involves a 2-stage approach. First, the induction phase (first 3-6 months) has the goal of rapidly quelling the inflammatory process and minimizing tissue damage. Second, the maintenance phase (the next 24-48 months) has the aim of preventing disease relapse. The standard of care for induction therapy in severe AAV includes a combination of glucocorticoids with either cyclophosphamide or rituximab. In patients with refractory disease, defined as no improvement or worsening disease activity by 4 to 6 weeks, it is recommended to switch the initial induction agent to the alternate agent: from cyclophosphamide to rituximab and vice versa. Thus, given the relapsing presentation of PR3-ANCA vasculitis in case 2, the best answer to question 2 would be (c) rituximab and glucocorticoids.

### Glucocorticoids

Glucocorticoids are a central component in the management of AAV, especially in the context of renal involvement, but are insufficient by themselves. For active AAV, current treatment guidelines suggest glucocorticoids beginning at high doses followed by a steroid taper. Patients with AAV with rapidly progressive GN or alveolar hemorrhage typically receive pulse methylprednisolone, 500 to 1,000 mg, daily for 3 days. Thereafter, oral prednisone is started at 1 mg/kg per day with a maximum of 60 to 80 mg daily and continued for 2 to 4 weeks, after which a prednisone taper is begun. There is no consensus on the best tapering regimen or duration of glucocorticoid therapy for AAV. In most trials, prednisone is either tapered to 5 to 10 mg at 6 months or treatment is discontinued at this time.

Although effective in controlling disease activity, there is a significant association between exposure to glucocorticoids and adverse effects. PEXIVAS, a recent large multicenter study of severe AAV (estimated GFR < 50 mL/min or pulmonary hemorrhage) has addressed the question of glucocorticoid dose for induction. This study

randomly assigned 704 patients in a 2 × 2 factorial design to plasma exchange or none and to standard-dose or low-dose glucocorticoid treatment (cumulative dose ~50% of standard group) on a background of cyclophosphamide or rituximab induction. There was no difference in efficacy between the 2 glucocorticoid groups, but a reduction in severe infections was seen in the first year in the low-dose glucocorticoid group. Although this study is not yet published, it is likely to dramatically change our use of glucocorticoids in AAV.

## Cyclophosphamide

AAV with organ and life-threatening manifestations has been treated with combination therapy of glucocorticoids and cyclophosphamide for decades. This regimen, although effective in >90% of patients, is limited by substantial toxicity. Cyclophosphamide can be given orally or intravenously and treatment is continued for 3 to 6 months until remission. The route of cyclophosphamide therapy was tested in the CYCLOPS trial, a randomized trial conducted by the European Vasculitis Study Group. CYCLOPS enrolled 149 patients with a new diagnosis of AAV and randomly assigned them to receive oral cyclophosphamide, 2 mg/kg per day, or intravenous cyclophosphamide, 15 mg/kg, every 2 to 3 weeks for 3 to 6 months. There was no difference in remission rates between the 2 groups, but the cumulative dose was higher in the oral cyclophosphamide group (16 vs 8 g) and intravenous cyclophosphamide was associated with fewer episodes of leukopenia. Long-term follow-up of CYCLOPS showed that although the oral cyclophosphamide group was at lower risk for relapse, presumably related to the higher cumulative dose, this did not translate into differences in renal or overall survival.

## Rituximab

Given the relapsing nature of AAV and the substantial toxicity associated with cumulative cyclophosphamide use, there has been a growing impetus to explore safer therapies targeting specific cellular and molecular pathways involved in the autoimmune response. Two randomized controlled trials, RAVE and RITUXVAS, evaluated the use of rituximab, a chimeric anti-CD20 monoclonal antibody, for remission induction in GPA and MPA. In the RAVE trial, patients with both new and relapsing GPA/MPA were enrolled (Scr < 4 mg/dL), the rituximab arm did not receive concurrent cyclophosphamide, and prednisone dosage was tapered to zero by month 6. The RITUXVAS trial enrolled only patients with newly diagnosed GPA/MPA with more severe kidney disease, including patients requiring dialysis. The rituximab arm also received 2 to 3 doses of intravenous cyclophosphamide and the use of plasmapheresis was allowed. The rituximab dose was 375 mg/m$^2$ once a week for 4 weeks in both trials. In both trials, rituximab was noninferior to cyclophosphamide for remission induction, with comparable rates of adverse events. In addition, the RAVE trial concluded that rituximab was superior to cyclophosphamide in patients with relapsing disease. In April 2011, rituximab was approved by the US Food and Drug Administration as an alternative to cyclophosphamide in combination with glucocorticoids for treatment of severe GPA/MPA. Rituximab is the preferred treatment for patients with relapsing disease, refractory disease, and those with contraindications to cyclophosphamide. In subgroup analysis, the RAVE trial demonstrated that rituximab was superior to cyclophosphamide for remission induction in patients with PR3-positive ANCA.

Rituximab dosed at 1,000 mg every 2 weeks for 2 doses, similar to the dosing in rheumatoid arthritis, has been demonstrated to produce reliable B-cell depletion with comparable outcomes at reduced cost. When rituximab is given to patients undergoing plasmapheresis, it is important to remember that there is considerable removal of rituximab by plasmapheresis. There are no guidelines concerning the optimal timing of rituximab administration after plasma exchange. In the PEXIVAS trial, plasma exchange was withheld for 48 hours after the initial rituximab dose.

## Mycophenolate Mofetil

A randomized controlled trial (MYCYC) evaluated the use of mycophenolate mofetil (MMF) for remission induction in AAV. This noninferiority trial randomly assigned patients with AAV with estimated GFRs > 15 mL/min/1.73 m$^2$ to intravenous cyclophosphamide or oral MMF (2-3 g/d). The primary end point for this trial, remission at 6 months, was achieved in 67% of patients in the MMF group compared to 61% in the cyclophosphamide group, demonstrating noninferiority. However, relapses were more common in the MMF group, mostly in PR3-ANCA–positive patients. This study suggests that MMF and glucocorticoids can be used as a first-line induction therapy in patients with MPO-ANCA who have mild to moderate renal involvement without life-threatening extrarenal vasculitis.

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## Novel Approaches to Remission Induction Therapy

### Combining Rituximab and Cyclophosphamide

Infection risk and its associated mortality remain a concern with both rituximab- and cyclophosphamide-based induction therapy. This is related to both the use of high doses of glucocorticoids and the rituximab/cumulative cyclophosphamide exposure. In an effort to decrease cyclophosphamide dose and minimize glucocorticoid exposure, 2 large observational studies reported results on the combined use of rituximab with lower dose cyclophosphamide (oral or intravenous) using a faster glucocorticoid taper. These studies demonstrated that the combination therapy induced remission in >80% of patients at 6 months and allowed for the use of lower glucocorticoid doses.

### Complement Inhibition

Identification of the role of complement in AAV has led to therapies targeting the alternative pathway and the anaphylatoxin C5a. In a phase 2 study, the selective C5a receptor inhibitor avacopan, given with and without low-dose steroid, was compared to standard-dose prednisone on a background of immunosuppression with either cyclophosphamide or rituximab. The avacopan groups were noninferior to the standard-prednisone group, highlighting a potential approach in which glucocorticoid doses can be minimized. A multicenter phase 3 trial of avacopan in AAV has recently completed enrollment, and the results are eagerly awaited.

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## Plasma Exchange

The basis for considering plasma exchange in AAV is that the removal of ANCAs and other inflammatory mediators can promote earlier reversal of the immunologic response and minimize tissue damage. The MEPEX trial examined the role of plasma exchange as adjuvant therapy to oral cyclophosphamide and glucocorticoids in patients with newly diagnosed AAV with severe kidney failure (Scr > 500 mmol/L [>5.7 mg/dL] or requiring dialysis at entry). At 12 months, there was a 24% risk reduction in progression to end-stage kidney disease; however, the longer-term follow-up data (median, 4 years) showed no difference in mortality or end-stage kidney disease. The unpublished PEXIVAS trial evaluated the role of plasma exchange in patients with severe AAV. By contrast, this study showed no difference in primary end points between the plasma exchange or no plasma exchange groups, and subgroup analysis failed to show a benefit in patients with pulmonary hemorrhage. When confirmed, these data will likely limit the use of plasma exchange in AAV, mostly to patients with combined AAV and anti-GBM disease.

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## Maintenance Therapy

***Case 2 (continued):*** *This 48-year-old woman with relapsing PR3-ANCA vasculitis was treated with rituximab and prednisone. She achieved remission at month 5 with resolution of microscopic hematuria and improvement in kidney function and resolution of lung infiltrates on follow-up CT of the chest. PR3-ANCA was negative at remission.*

**Key questions:**
- What is the risk for relapse for this patient?
- What is the maintenance immunosuppressive agent of choice for this patient?
- How long should maintenance immunosuppression be continued?

Advances in induction therapy have transformed AAV from a life-threatening disease to a chronic illness with a relapsing course. Relapse is common, occurring in 30% to 50% of patients by 5 years in older studies, often in the 12 to 18 months after immunosuppression treatment is discontinued. Risk factors for relapse include PR3-ANCA serotype; GPA phenotype; preserved kidney function; involvement of ear, nose, and throat; lower cumulative cyclophosphamide dose for induction therapy; and

**Box 2.** Risk Factors for Relapse of ANCA-Associated Vasculitis

**Demographics**
- Younger patients

**ANCA**
- PR3-ANCA disease
- Persistence of ANCA after induction therapy
- Increase in ANCA titers (more predictive of renal relapse)

**Clinical phenotype**
- GPA
- Lung, upper respiratory tract, or cardiac involvement
- Preserved kidney function
- Prior relapses

**Therapy related**
- Discontinuation of immunosuppression (short duration of treatment)
- Lower cumulative dose of cyclophosphamide
- Discontinuation of prednisone
- Use of MMF for maintenance therapy
- B-cell reconstitution post rituximab

**Other factors**
- Chronic nasal carriage of *Staphylococcus aureus*
- HLA-DP1*04 alleles (in PR3-ANCA disease)

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; GPA, granulomatosis with polyangiitis; MMF, mycophenolate mofetil; PR3, proteinase 3.

withdrawal of glucocorticoid treatment (Box 2). Prevention of relapse is paramount to maintain patient quality of life and prevent disease- and treatment-related morbidity and mortality. The use of maintenance immunosuppression for relapse prevention following successful remission induction is standard. The only exception to this would be patients presenting with dialysis for renal-limited vasculitis who do not respond to induction therapy and have reached kidney failure. This is justified because patients with AAV who reach kidney failure have lower rates of vasculitis relapse and a higher infection risk.

Randomized controlled trials have confirmed the efficacy of cyclophosphamide-sparing agents for remission maintenance in AAV. In the CYCAZAREM trial, patients with AAV who achieved remission with oral cyclophosphamide were randomly assigned to continue cyclophosphamide therapy or switch to azathioprine at 6 months. At 18 months, relapse rates were similar. The IMPROVE trial compared MMF to azathioprine and showed higher rates of relapse in patients treated with MMF. MMF may still be considered for remission maintenance in patients who have intolerance to azathioprine.

Recent studies have assessed the role of rituximab for maintenance therapy and have shown dramatically lower rates of relapse. The MAINRITSAN trial compared patients in remission receiving azathioprine with a series of 5 rituximab infusions (500 mg) over 18 months. This trial demonstrated superiority of rituximab, with only 5% of treated patients experiencing a major relapse compared to 29% in the azathioprine arm. The long-term follow-up of this trial confirmed that the superiority of rituximab was maintained at 60 months. The MAINRITSAN 2 trial compared fixed-dose rituximab dosing (500 mg on days 0 and 14 and months 6, 12, and 18) with rituximab dosing tailored to B-cell reappearance (CD19 count > 0) and ANCA titers (reappearance or doubling). At 28 months, there was no difference in relapse or adverse events between the 2 groups, but the median number of infusions was reduced in the tailored group (3 vs 5). It is important to note that all maintenance therapies in AAV to date have compared different maintenance regimens in patients treated with cyclophosphamide for remission induction. The ongoing RITAZAREM trial (ClinicalTrials.gov identifier NCT01697267) addresses this by comparing rituximab (1,000 mg every 4 months for 2 years) with conventional maintenance therapy with azathioprine in patients with relapsing AAV who received rituximab for induction.

The optimal duration of maintenance immunosuppression is debated despite the refinement of maintenance therapy strategies guided by randomized controlled trials during the past 2 decades. Long-term follow-up of maintenance therapy trials have shown higher relapse rates after discontinuation of immunosuppressive therapy. A retrospective study from the Cleveland Clinic demonstrated that patients with GPA treated with azathioprine or methotrexate for more than 36 months reduced the hazard ratio for relapse by 66% compared to 29% reduction in those treated for 18 to 36 months and provided compelling support for the use of longer maintenance therapy.

The REMAIN trial is a randomized controlled trial that tested whether continuing azathioprine and prednisone treatment for 48 months was more effective in relapse prevention than withdrawal at 24 months. Results from this study showed a significant decrease in both major and minor relapses and better renal survival in the continuation group. However, major relapses occurred in only 35% of patients in the withdrawal group, suggesting that two-thirds of patients did not require prolonged maintenance therapy. Accordingly, a decision to extend maintenance immunosuppressive therapy duration should be personalized based on predictors of relapse such as ANCA serotype, ANCA status at remission, organ involvement, kidney function, and intensity of induction therapy. Trials assessing the duration of rituximab maintenance therapy have not been performed.

A proposed algorithm for the treatment of ANCA GN is shown in Figure 4.

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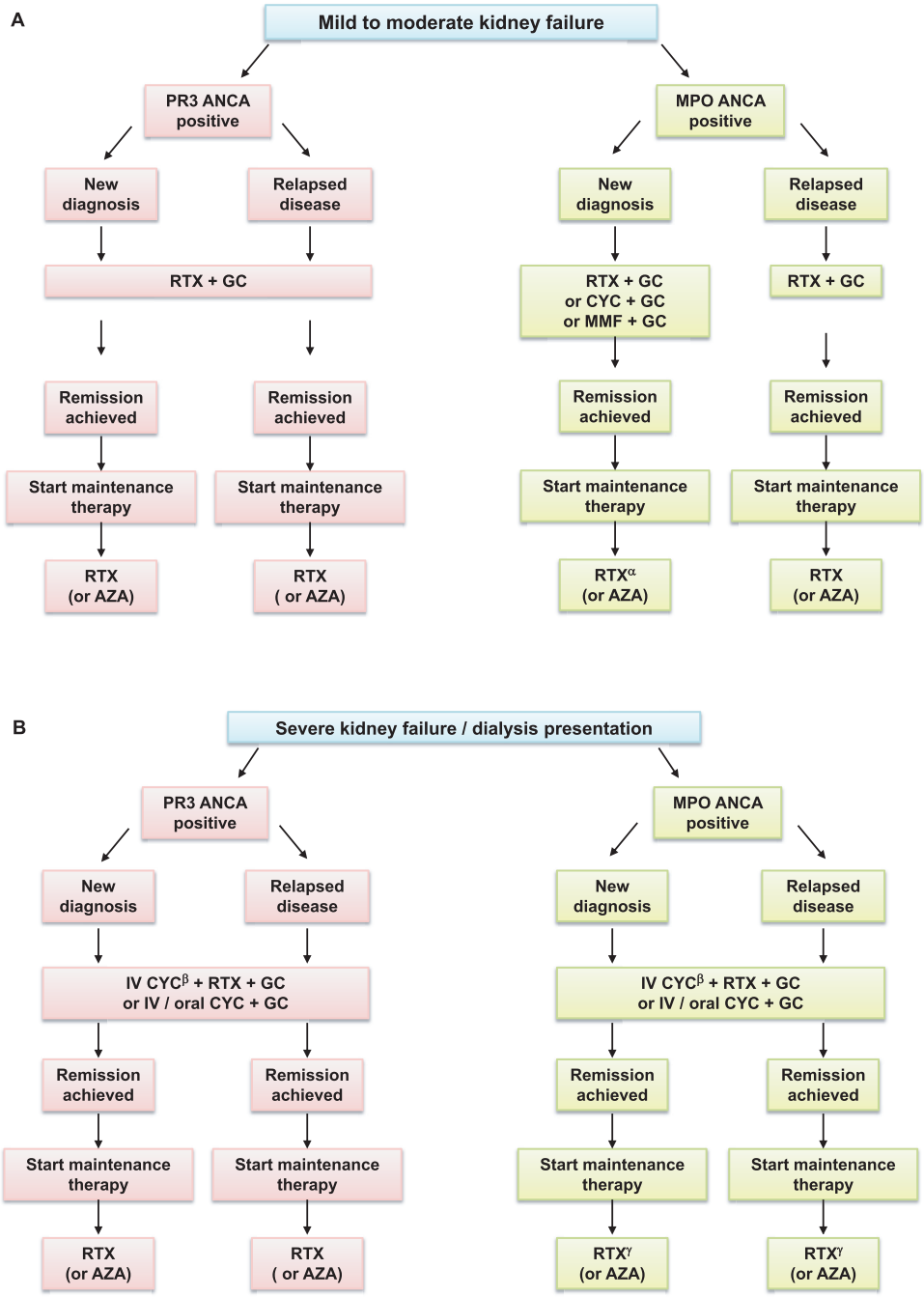


**Figure 4.** (A, B) Proposed treatment algorithm for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. [α]Maintenance therapy should be individualized according to the risk for relapse. Patients with myeloperoxidase (MPO)-ANCA have a lower relapse risk and a shorter duration (18-24 months) of therapy may be appropriate after initial presentation. [β]Data are limited in patients with advanced kidney failure at presentation; the authors prefer a cyclophosphamide (CYC)-based regimen, such as that used in the RITUXVAS trial in this setting. [γ]Patients who have reached end-stage kidney disease and have no extrarenal manifestations may not require maintenance immunosuppression. Abbreviations: AZA, azathioprine; GC, glucocorticoids; MMF, mycophenolate mofetil; PR3, proteinase 3; RTX, rituximab.

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## Monitoring and Management of Disease and Treatment-Related Complications

The survival of patients with AAV has greatly improved since the use of cyclophosphamide for induction therapy. Despite this, the mortality of patients with AAV remains 2 to 3 times greater than for the age- and sex-matched general population. Side effects from immunosuppressive therapy now account for the majority of early mortality in AAV, while infection, malignancy, and cardiovascular disease are causes of late mortality.

### Screening and Prophylaxis

Before starting therapy with immunosuppression, screening for hepatitis B virus, hepatitis C virus, HIV, latent tuberculosis, and strongyloides is recommended. Patients should be vaccinated according to latest Centers for Disease Control and Prevention guidelines for immunocompromised patients, including inactivated pneumococcal, influenza, and HBV vaccines, but avoiding live vaccines such as the attenuated varicella-zoster virus vaccine (marketed as Zostavax in the United States). A new inactivated recombinant zoster vaccine became available in the United States in 2017.

Prophylaxis for *Pneumocystis jirovecii* pneumonia is recommended for all patients receiving induction therapy with prednisone and cyclophosphamide or rituximab. There is no consensus on when to stop *P jirovecii* pneumonia prophylaxis in patients with AAV, but some will discontinue prophylaxis when the oral prednisone dose is <20 mg/d. Trimethoprim-sulfamethoxazole is most commonly used, but alternate agents include dapsone, inhaled pentamidine, and atovaquone. Candida prophylaxis with clotrimazole troche or weekly oral fluconazole should be considered in patients treated with high-dose glucocorticoids. Calcium, vitamin D, and a Fracture Risk Assessment Tool (FRAX) risk assessment should be considered for prevention of steroid-induced osteoporosis (Box 3).

**Box 3.** Screening and Prophylaxis in ANCA-Associated Vasculitis

**Vaccination**
- Per CDC guidelines, including inactivated pneumococcal, influenza, and hepatitis B vaccines, but avoiding live vaccines

**Infection Screening**
- Hepatitis B: HBsAg, anti-HBc antibody
- Hepatitis C: anti-HCV antibody
- HIV: anti-HIV antibody ± HIV p24 antigen
- Latent TB: chest x-ray, tuberculin skin test (TST), or interferon-gamma release assay (IGRA)
- Strongyloides: anti-strongyloides antibody

**Infection Prophylaxis**
- *Pneumocystis jirovecii*: co-trimoxazole or dapsone, atovaquone, inhaled pentamidine
- Candida: clotrimazole troche or weekly fluconazole

**Other Prophylaxis**
- Osteoporosis: calcium and vitamin D; ± bisphosphonates
- Gastroprophylaxis: histamine ($H_2$) antagonist, proton pump inhibitor

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; anti-HBc, hepatitis B core antobody; CDC, Centers for disease Control and Prevention; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TB, tuberculosis.

## Specific Side Effects of Immunosuppression

### Cyclophosphamide-Specific Side Effects

Cyclophosphamide is associated with multiple serious adverse effects; many happen early (bone marrow suppression, infection, hemorrhagic cystitis, and infertility), but others may arise 10 or more years after conclusion of immunotherapy (malignancy). Leukopenia correlates with the risk for infection, and a complete blood cell count should be checked every 2 weeks during treatment with oral cyclophosphamide, and the dose should be adjusted to maintain a leukocyte count $> 3.5 \times 10^9$ cells/L. For patients receiving intravenous cyclophosphamide, complete blood cell count should be checked 10 to 14 days after each pulse. Patients receiving intravenous cyclophosphamide may also receive mesna to protect the bladder from acrolein toxicity resulting in hemorrhagic cystitis.

The risk for primary ovarian failure is linked to the cumulative dose of cyclophosphamide, and ovarian suppression with gonadotropin-releasing hormone agonists (eg, leuprolide) is often used for protection, but efficacy is debated. In men, the risk for permanent azoospermia increases with cumulative dose (especially >10 g) and semen cryopreservation should be considered. Cyclophosphamide is associated with an increased incidence of malignances (usually skin cancer, myeloid malignancies, and bladder cancer), especially when the cumulative dose is >36 g.

### Rituximab-Specific Side Effects

In the RAVE and RITUXVAS trials, severe infection was described in 7% and 18%, respectively, and surprisingly was not reduced compared to the cyclophosphamide arm, possibly due to the high-dose glucocorticoids in both groups. Hepatitis B virus reactivation and hepatic flares in hepatitis C virus–positive patients are observed in patients treated with rituximab. Progressive multifocal

leukoencephalopathy is a very rare complication of rituximab therapy that may be more common in patients exposed to other immunosuppressive agents. Infection risk may also be increased with hypogammaglobulinemia, which occurs in 50% of patients with AAV treated with rituximab but is rare in other diseases. In most instances, the hypogammaglobulinemia is mild largely due to the establishment of long-lived plasma cells that are resistant to rituximab and are able to maintain the IgG pool. Severe hypogammaglobulinemia (less than 3-4 g/L) occurs in a minority of patients, but ~5% experience recurrent infections requiring the use of intravenous immunoglobulin. Low baseline immunoglobulin level, prior cyclophosphamide exposure, and glucocorticoid therapy are recognized as risk factors for rituximab-induced hypogammaglobulinemia. Immunoglobulin levels should be checked at baseline and before each rituximab infusion. Late-onset neutropenia is a rare side effect of rituximab that manifests as abrupt and often severe neutropenia. It usually occurs 2 to 6 months following the last dose of rituximab and recovers spontaneously, but may take several months. It is typically asymptomatic, but filgrastim may be considered when associated with infection.

### Glucocorticoid-Related Toxicity

Glucocorticoids have an extensive side-effect profile, including infection, bone disease, dysglycemia, obesity, hypertension, psychosis, gastrointestinal bleeding, cataracts, adrenal suppression. and long-term risks for cardiovascular disease. In older studies of patients with AAV treated with glucocorticoids, common adverse events reported included weight gain > 10 kg (29%), new-onset diabetes (8.2%), peptic ulcer disease (2.6%), fractures (2.5%), and avascular necrosis (0.4%); and during long-term follow-up, cataracts (25%), diabetes (38%), osteoporosis (38%), and hypertension (41%). In view of the severity and frequency of these adverse effects, recent trials are focusing on steroid-sparing approaches such as lower dose glucocorticoid regimens (PEXIVAS study) and complement inhibition (avacopan study).

### Cardiovascular Disease

Inflammation, use of glucocorticoids, and decreased kidney function accelerate the development of hypertension, diabetes, weight gain, and hyperlipidemia and contribute to increased cardiovascular risk in patients with AAV. Long-term data from European patients with vasculitis showed that 14% of patients with AAV experience a cardiovascular event within 5 years of diagnosis. Precise assessment and management of cardiovascular risk factors are required.

### Malignancy

Malignancy is a grave consequence of immunosuppressive therapy. The risk for malignancy is significantly higher in patients with AAV compared to the general population, with a standardized incidence rate of 1.74, in particular, in patients treated with higher dose cyclophosphamide (>36 g cumulative exposure). Bladder carcinoma, nonmelanoma skin cancer, and leukemia are the most commonly reported malignancies. Azathioprine use is strongly associated with nonmelanoma skin cancers. The malignancy risk with rituximab is similar to the general population.

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## Management of Dialysis and Kidney Transplantation

### Dialysis

Renal prognosis remains suboptimal in AAV despite advances in treatment, and 20% to 25% of patients reach kidney failure. Relapse rates are low in patients receiving dialysis (0.08 episode per person per year), and consideration for withdrawal of immunosuppression may be considered after 6 months in those with no extrarenal manifestations, especially MPO-ANCA serotype. An ongoing study, MASTER-ANCA, will address this question. Patients with AAV are more likely to receive hemodialysis compared to peritoneal dialysis and the mortality rate is similar to other nondiabetic nephropathies.

### Kidney Transplantation

Kidney transplantation remains the treatment of choice for kidney failure in patients with AAV due to improved quality of life and survival advantage. With the use of modern transplant immunosuppressive regimens, vasculitis relapse rates are low, ranging from 0.01 to 0.02 episode per patient per year. Although the presence of stable ANCA titers is not a contraindication to kidney transplantation, KDIGO (Kidney Disease: Improving Global Outcomes) and Canadian transplantation guidelines recommend that patients should be in clinical remission for 12 months before proceeding.

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