

ANCA-Associated Vasculitis: Diagnosis, Classification, and Treatment

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Classification: Three Phenotypes

ANCA-associated vasculitis (AAV) accounts for ~50% of pulmonary-renal syndrome cases. Three clinically and serologically distinct entities:

Phenotype	ANCA Type	Associated Antigen	Prevalence	Key Features
GPA (Granulomatosis with Polyangiitis, formerly Wegener granulomatosis)	c-ANCA	Proteinase 3 (PR3)	40-50% of AAV	Upper resp tract granulomas, pulmonary nodules, necrotizing GN
MPA (Microscopic Polyangiitis)	p-ANCA	Myeloperoxidase (MPO)	40-50% of AAV	Pulmonary-renal syndrome, minimal extra-pulmonary involvement, necrotizing GN

Phenotype	ANCA Type	Associated Antigen	Prevalence	Key Features
EGPA (Eosinophilic Granulomatosis with Polyangiitis, formerly Churg-Strauss)	p-ANCA (50%)	MPO or ANCA-negative	10-15% of AAV	Asthma, eosinophilia, cardiac/GI involvement, later-onset vasculitis

[!important] Key Point **Serology-pathology mismatch:** Don't diagnose by serology alone. Biopsy remains gold standard. ~10% of confirmed AAV are ANCA-negative (especially EGPA).

Epidemiology & Presentation

Age & Demographics

- **Peak incidence:** 50-70 years old
- **GPA:** Slightly younger, more common in Whites
- **MPA:** Slightly older, no racial predominance
- **EGPA:** Most common in 40-50 year-olds

ANCA-Associated Vasculitis Clinical Spectrum

GPA (Granulomatosis with Polyangiitis) - Upper respiratory tract (90%): Sinusitis, nasal granulomas, saddle nose deformity - **Lungs** (85%): Nodules (often cavitary), infiltrates, hemoptysis - **Kidneys** (80%): RPGN, hematuria, RBC casts - **Other:** Eyes (scleritis), skin (palpable purpura), joints (arthritis), CNS (rare)

MPA (Microscopic Polyangiitis) - NO upper respiratory involvement (distinguishes from GPA) - **Lungs** (85%): Pulmonary hemorrhage (hemoptysis, pulmonary edema) - **Kidneys** (100%): RPGN (diagnostic hallmark) - **Skin** (40%): Palpable purpura, necrotizing vasculitis - **GI** (20%): Abdominal pain, bleeding - **Systemic:** Constitutional symptoms (fever, weight loss, arthralgia)

EGPA (Eosinophilic Granulomatosis with Polyangiitis) - Prodrome: Asthma (>90%), usually 5-10 years before vasculitis - **Eosinophilia:** Marked peripheral eosinophilia ($>1.5 \times 10^9/L$) diagnostic - **Cardiac** (50%): Myocarditis, pericarditis, heart failure - **GI** (60%): Abdominal pain, ischemia, perforation - **Neuropathy** (70%): Mononeuritis multiplex, distal symmetric polyneuropathy - **Kidneys** (40%): RPGN, but less severe than GPA/MPA; glomerulonephritis more pauci-immune

Pathophysiology: ANCA-Mediated Vascular Injury

The Four-Hit Model

Hit 1: Abnormal Neutrophil Priming - Genetic susceptibility genes (HLA-DPA1, HLA-DPB1, PR3, PRTN3 loci) - Environmental triggers (infections, drugs like hydralazine, propylthiouracil) - Neutrophils primed to express ANCA antigens on surface

Hit 2: ANCA Autoantibody Production - B cells produce anti-PR3 (c-ANCA, GPA) or anti-MPO (p-ANCA, MPA) - IgG1/IgG3 subclasses activate complement - Serum ANCA titer correlates with disease activity (especially PR3)

Hit 3: Neutrophil Activation & Degranulation - ANCA IgG crosslinks surface PR3/MPO → neutrophil activation - Fc receptor engagement amplifies activation - Neutrophil extracellular traps (NETs) release enzymes, exacerbating inflammation

Hit 4: Vascular Injury - Necrotizing vasculitis of small arteries, capillaries, venules - Direct endothelial injury from serine proteases (PR3, NE) - Complement activation (C5a, MAC), monocyte recruitment - Glomerular crescent formation if renal involvement

Diagnosis: Biopsy + ANCA Testing

ANCA Serology

c-ANCA (Cytoplasmic Pattern)

- **Antigen:** Proteinase-3 (PR3)
- **Association:** GPA (>90%), rarely MPA
- **Method:** Indirect immunofluorescence (staining pattern) + ELISA (antigen confirmation)
- **Specificity:** 95-99% if positive
- **Sensitivity:** 90% in generalized GPA; <50% in localized disease (confined to upper resp)

p-ANCA (Perinuclear Pattern)

- **Antigen:** Myeloperoxidase (MPO)
- **Association:** MPA (90%), EGPA (50%), vasculitis-associated GN
- **Specificity:** 95-99% if positive
- **Sensitivity:** 80% in MPA, 50% in EGPA

ANCA-Negative AAV

- ~10% of confirmed AAV cases (especially EGPA)
- Diagnosis: Clinical features + compatible pathology on biopsy
- Don't exclude AAV if high suspicion and negative ANCA

[!warning] High-Yield Board Point **Drug-induced ANCA vasculitis:** Hydralazine, propylthiouracil (PTU), sulfasalazine, minocycline → MPO-ANCA vasculitis (typically p-ANCA). Discontinue drug; vasculitis usually resolves without immunosuppression over weeks-months.

Kidney Biopsy (Gold Standard for Renal Involvement)

Light Microscopy: - **Segmental fibrinoid necrosis** (crescent formation) - **Necrosis of capillary wall** without immune complex deposition - **Crescent types:** Cellular (early, reversible), fibrocellular (intermediate), fibrous (end-stage, irreversible) - **Pauci-immune pattern** (minimal immune complex)

Immunofluorescence: - **Pauci-immune** (minimal IgG, IgM, IgA, C3) - Hallmark of ANCA-GN - C3 may be present if secondary complement activation - **Full-house IF** rules OUT AAV, suggests lupus instead

Electron Microscopy: - **Minimal electron-dense deposits** (pauci-immune) - Rarefaction of capillary wall, fibrin material

Other Diagnostic Clues

Test	Findings	Significance
CBC	Anemia (chronic disease), elevated WBC if active	Non-specific
CMP	Elevated Cr, AKI pattern	GN activity
UA	Hematuria, RBC casts, proteinuria	GN activity
Chest X-ray	Pulmonary nodules (GPA), infiltrates (MPA/EGPA), eosinophilic infiltrates (EGPA)	Often diagnostic for GPA
ESR/CRP	Markedly elevated	Indicates inflammation; high ESR predicts relapse
Complement	Normal (hallmark)	Helps distinguish from lupus (low complement)
Cryoglobulins	Negative	Distinguishes from mixed cryoglobulinemia

ANCA-Associated GN Classification (Pathologic Findings)

Class	% Glomeruli Sclerosed	% Glomeruli with Crescents	Prognosis	Treatment
Focal	<50%	<50%	Best	Standard induction

Class	% Glomeruli Sclerosed	% Glomeruli with Crescents	Prognosis	Treatment
Crescentic	<50%	50-75%	Intermediate	Aggressive induction
Sclerotic	>50%	Variable	Worst	Supportive care, no reversal expected

[!warning] High-Yield Board Point **Sclerotic ANCA-GN**: If >80% of glomeruli sclerosed at biopsy, prognosis for renal recovery poor. Immunosuppression unlikely to help; focus on preventing further deterioration.

Treatment Algorithm

Remission Induction (3-6 Months)

Goal: Achieve complete remission (Cr stable, UA normalized, ANCA becoming negative or titer declining, no systemic symptoms).

Standard Induction: Rituximab Preferred (RAVE Trial) **RAVE Trial** (2010): Rituximab equivalent to cyclophosphamide for induction; preferred due to fewer infertility/infection risks [1]

Rituximab-based induction: - **Rituximab:** 1000 mg IV $\times$ 2 infusions 2 weeks apart (or 375 mg/m² weekly $\times$ 4 weeks) - **Corticosteroids:** IV methylprednisolone 1000 mg $\times$ 3 days (or 500-750 mg/day $\times$ 3 days), then prednisone 1 mg/kg daily (max 80 mg) taper over 3-6 months to 5-10 mg/day - **Induction duration:** 3-6 months to remission

Advantages: - Non-inferior to cyclophosphamide for remission rates (~90%) - Less infertility risk (especially in women) - Fewer infections - Can repeat doses if relapse

Monitoring: - Monthly: CBC (CD19 cells should become undetectable), ANCA titer, Cr, UA - Assess for sterile pyuria, infections

Alternative Induction: Cyclophosphamide (If Rituximab Contraindicated) **NIH vs Euro-Lupus Dosing:** - **NIH:** 500-1000 mg/m² IV monthly $\times$ 3-6 months - **Euro-Lupus:** 500 mg fixed dose IV monthly $\times$ 6 months (equivalent efficacy, lower cumulative toxicity)

Corticosteroids: Same as rituximab regimen above

Monitoring: Monthly CBC, Cr, UA; mesna prophylaxis (0.6 mg per mg CYC) for hemorrhagic cystitis

Complementary Therapy

Complement Inhibition (Avacopan) ADVOCATE Trial (2021): Avacopan (C5a receptor antagonist) added to standard induction → faster remission, steroid-sparing [2]

Avacopan dosing: - 150 mg orally twice daily × 12 weeks induction (or 24 weeks maintenance)
- Mechanism: Blocks C5a (complement amplification loop); reduces crescent formation

Benefits: - Faster proteinuria resolution - Reduced steroid exposure (taper faster) - Useful if serum creatinine >1.5 mg/dL (steroid + rituximab alone slower)

Cost/Access: Expensive; use if available or severe disease

Remission Maintenance (≥18-24 Months)

Goal: Maintain remission on minimal immunosuppression to prevent relapse (50% risk without maintenance) while minimizing long-term toxicity.

Rituximab-Based Maintenance

- **Fixed-schedule rituximab:** 500 mg IV every 6 months (MAINRITSAN trials)
- **Alternative:** Rituximab doses based on B-cell recovery (CD19 reappearance)
- **Duration:** Minimum 18-24 months; some trials used ≥3 years
- **Prednisone:** Taper to 5-7.5 mg daily (continue indefinitely at low dose)

Azathioprine-Based Maintenance (Older Standard)

- **Azathioprine:** 1.5-2.5 mg/kg daily
- **Prednisone:** 5-10 mg daily
- **Duration:** ≥18-24 months (≥2 years preferred)
- **Disadvantage:** Higher relapse rates than rituximab
- **Use if:** Rituximab contraindicated or cost prohibitive

Maintenance Without Rituximab Infusions

- If CYC used for induction, switch to azathioprine or MMF for maintenance

Special Scenarios

ANCA-GN with Pulmonary Hemorrhage

- **Immediate life threat:** Hemoptysis + hypoxia
- **Management:**
 - Urgent immunosuppression (induction as above)
 - Consider **plasma exchange** (debate persists, but some benefit if Hb <7 or O₂ requirement high)
 - High-dose IV methylprednisolone 1000 mg × 3-7 days
 - Intubation if severe respiratory failure

- **PEXIVAS Trial (2020):** Plasma exchange + immunosuppression vs. immunosuppression alone — **no significant difference in primary outcome** (ESRD/death), but trend toward benefit in fulminant presentations [3]

ANCA-Negative Pauci-Immune RPGN

- ~10% of pauci-immune RPGN are ANCA-negative
- **Diagnosis:** Clinical features + biopsy findings (pauci-immune crescents)
- **Treatment:** Same as ANCA+ RPGN
- **Prognosis:** Variable; some respond well, others more aggressive

Localized GPA (Upper Respiratory Only)

- **No systemic/renal involvement** at diagnosis
- **ANCA:** Often negative or low-titer c-ANCA
- **Management:** Observation or low-dose rituximab (rituximab 375 mg/m² × 4 weeks)
- **Close follow-up:** Monitor for systemic progression (monthly UA, Cr, ANCA)
- **Risk of progression:** 50% progress to generalized disease if untreated

Relapsing ANCA Vasculitis

- **40-50% relapse rate** during or after maintenance therapy
- **Predictors of relapse:** PR3-ANCA (higher risk), persistent ANCA seropositivity, male sex
- **Management:**
 - If on maintenance rituximab: Increase frequency (q 4 months vs. q 6 months)
 - If on azathioprine: Switch to rituximab maintenance
 - Assess adherence to medications
 - Exclude infection, drug-induced vasculitis

Clinical Pearls & Pitfalls

[!tip] Clinical Pearl **ANCA-negative pauci-immune RPGN:** Don't miss these! 10-15% of confirmed AAV are ANCA-negative. Biopsy is diagnostic. Clinical features + pauci-immune crescents sufficient for diagnosis and treatment initiation.

[!warning] High-Yield Board Point **PR3-ANCA vs. MPO-ANCA relapse risk:** PR3-ANCA (GPA) patients have ~50% relapse risk; MPO-ANCA (MPA) have ~30% relapse risk. Higher relapse risk in PR3 justifies longer maintenance (2-3 years vs. 18 months).

[!important] Key Point **Monitoring ANCA titers:** Persistently positive or rising ANCA during remission predicts imminent relapse. However, negative ANCA doesn't exclude relapse (15% of relapses are ANCA-negative). Monitor clinical features more than serology.

[!tip] Clinical Pearl **EGPA cardiac involvement:** Myocarditis with reduced EF is ominous sign in EGPA. Requires intensive induction (CYC often preferred over rituximab if severe cardiac disease). Echocardiography baseline screening recommended.

[!warning] High-Yield Board Point **Infection risk with rituximab induction:** Opportunistic infections (PCP, CMV, listeria) can occur during B-cell depletion. Screen for TB; consider PCP prophylaxis (TMP-SMX) if CD4 <500. Monitor for symptoms closely.

Landmark Trials

[1] **RAVE Trial** (2010): Rituximab vs. cyclophosphamide for ANCA-associated vasculitis induction. *NEJM*. 2010;363(3):221–232. PMID: 20647200

[2] **ADVOCATE Trial** (2021): Avacopan + standard induction vs. standard induction alone. *NEJM*. 2021;384(7):599–609. PMID: 33630041

[3] **PEXIVAS Trial** (2020): Plasma exchange + immunosuppression vs. immunosuppression in ANCA vasculitis with severe renal failure. *NEJM*. 2020;382(7):622–631. PMID: 32109232

Related Resources

- RPGN Diagnostic Algorithm
 - Glomerular Disease Diagnostic Algorithm
 - CKD Comprehensive Management Pathways
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