Vasculitis and Complement-Mediated Glomerulonephritis: ANCA, Anti-GBM, and C3 Diseases

Andrew Bland, MD, FACP, FAAP

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Learning Objectives

By the end of this handout, students will be able to:

1. **Classify vasculitis** by vessel size (large, medium, small) and understand which diseases cause glomerulonephritis
2. **Explain the pathophysiology** of ANCA-associated vasculitis (AAV), distinguishing GPA, MPA, and EGPA
3. **Understand anti-GBM disease** (Goodpasture syndrome) pathophysiology and clinical presentation
4. **Recognize C3 glomerulopathy** and its forms (C3GN, dense deposit disease/MPGN-IC)
5. **Apply the complement cascade** (classical, lectin, alternative pathways) and understand which pathway(s) drive each disease
6. **Interpret serologic testing algorithms:** ANA, ANCA (c-ANCA, p-ANCA), anti-GBM, complement levels (C3, C4), and light microscopy patterns
7. **Manage acute vasculitis** and recognize indications for immunosuppression vs. supportive care

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I. Classification of Vasculitis Involving the Kidney

Vessel Size and Associated Diseases

Large-Vessel Vasculitis (Aorta, Major Branches) - Takayasu arteritis (large arteries in young women; Asian predominance) - Giant cell (temporal) arteritis (>50 years; cranial vessels) - Polyarteritis nodosa (medium, not typically glomerulonephritis) - **Renal involvement:** Uncommon in glomerulonephritis; more often renal artery stenosis

Medium-Vessel Vasculitis - Polyarteritis nodosa (PAN) — small to medium arteries, NOT glomerulonephritis - Kawasaki disease (medium arteries in children; Japan) - **Renal involvement:** Uncommon glomerulonephritis; more often renal artery disease

Small-Vessel Vasculitis (Glomeruli, Arterioles, Small Arteries)

Disease	ANCA	Anti-GBM	Immune Complex	Pathology
ANCA-Associated Vasculitis (AAV)	Yes	No	No (pauci-immune)	Necrotizing GN + necrotizing vasculitis
Granulomatosis with Polyangiitis (GPA)	c-ANCA/PR3	No	No	Necrotizing GN + granulomas
Microscopic Polyangiitis (MPA)	p-ANCA/MPO	No	No	Necrotizing GN without granulomas
Eosinophilic Granulo-matosis with Polyangiitis (EGPA)	p-ANCA/MPO (40–60%)	No	No	Necrotizing GN + eosinophilic infiltrates
Anti-GBM Disease	No (usually)	Yes	No	Linear IgG on GBM
Immune Complex Vasculitis	No	No	Yes	Immune deposits
IgA Vasculitis (IgAN)	No	No	Yes	IgA deposits
Membranoproliferative GN (MPGN) with IC	No	No	Yes	C3, Ig deposits
Lupus Nephritis (SLE)	No	No	Yes	Multi-Ig deposits

Focus of this handout: ANCA-associated vasculitis, anti-GBM disease, and C3-complement-mediated diseases.

II. ANCA-Associated Vasculitis (AAV)

Definition and Epidemiology

ANCA-associated vasculitis (AAV) is a **pauci-immune, systemic, small-vessel necrotizing vasculitis** characterized by: - **Circulating ANCA** (antineutrophil cytoplasmic antibodies) - **Glomerulonephritis** (necrotizing, pauci-immune pattern on immunofluorescence) - **Pulmonary and systemic involvement** depending on ANCA subtype

Incidence: 10–15 per million per year in Northern Europe/North America

Age of onset: Bimodal (peaks at 40–50 and 60–70 years)

Three Main Forms of AAV

1. Granulomatosis with Polyangiitis (GPA) — Formerly Wegener's Granulomatosis ANCA type: c-ANCA (cytoplasmic pattern), anti-PR3 (proteinase 3) in 90%

Classic triad: 1. **Upper respiratory tract:** Sinusitis, nasal granulomas, saddle nose deformity, epistaxis 2. **Lower respiratory tract:** Pulmonary nodules (often cavitary), hemoptysis, dyspnea 3. **Glomerulonephritis:** Rapidly progressive renal failure (RPGN), hematuria, proteinuria

Extra-articular features: - Ocular involvement (episcleritis, scleritis, uveitis, retro-orbital mass) - Skin: Palpable purpura, nodules, ulcers - Joints: Arthralgia, non-erosive arthritis - Nervous system: Mononeuritis multiplex, cranial nerve involvement - Constitutional: Fever, weight loss, malaise

Pathology (hallmark): - **Necrotizing vasculitis** (medium and small vessels) - **Necrotizing glomerulonephritis** (crescent formation) - **GRANULOMAS** (eosinophilic necrosis surrounded by histiocytes) — distinguishes from MPA - Pauci-immune immunofluorescence (minimal or no Ig/complement)

Prognosis without treatment: Rapidly progressive renal failure; mortality high if untreated.

2. Microscopic Polyangiitis (MPA) ANCA type: p-ANCA (perinuclear pattern), anti-MPO (myeloperoxidase) in 80–90%

Clinical presentation: - **Primarily renal and pulmonary** (no upper respiratory involvement) - **Rapidly progressive glomerulonephritis** (same appearance as GPA glomerularly, but NO granulomas) - Pulmonary hemorrhage (hemoptysis, dyspnea) - Systemic symptoms: Fever, weight loss, arthralgia - **Skin, joints, nervous system** involvement less common than GPA

Pathology (hallmark): - **Necrotizing vasculitis** (small vessels and capillaries) - **Necrotizing glomerulonephritis** (indistinguishable from GPA) - **NO granulomas** (key distinguishing feature from GPA) - Pauci-immune pattern

Epidemiology: Often older than GPA; slightly more common than GPA globally.

Prognosis: Similar to GPA if untreated; responsive to immunosuppression.

3. Eosinophilic Granulomatosis with Polyangiitis (EGPA) — Formerly Churg-Strauss Syndrome ANCA type: p-ANCA (anti-MPO) in 40–60%; 40–60% ANCA-negative ("seronegative EGPA")

Classic triad: 1. **Asthma/allergies:** History of asthma (often adult-onset), rhinosinusitis, allergic rhinitis 2. **Eosinophilia:** Peripheral blood eosinophilia (>1,500/μL or >10% WBC), often prominent 3. **Systemic vasculitis:** Palpable purpura (lower extremities), mononeuritis multiplex, abdominal pain, cardiac involvement

Extra-articular features: - **Cardiac involvement:** Cardiomyopathy (from myocardial infiltration), pericarditis, coronary vasculitis (unique among ANCA diseases) - **GI involvement:**

Mesenteric ischemia, abdominal pain (from mesenteric vasculitis) - **Pulmonary:** Infiltrates, pulmonary hemorrhage - **Nervous system:** Mononeuritis multiplex (common), other neuropathies - **Skin:** Palpable purpura, nodules

Pathology (hallmark): - **Necrotizing vasculitis** (small and medium vessels) - **Necrotizing and crescentic glomerulonephritis** (less common than GPA/MPA; milder disease overall) - **EOSINOPHIL-RICH INFILTRATES** (key distinguishing feature) - Granulomas possible but less prominent than GPA - Pauci-immune or necrotizing pattern

Epidemiology: Rare; intermediate between GPA and MPA in severity.

Prognosis: Often milder than GPA/MPA regarding renal disease, but cardiac involvement can be life-threatening.

Pathophysiology of AAV

ANCA-Antigen Interaction and Neutrophil Activation:

1. **ANCA production:** Immune response to ANCA antigens (PR3 in GPA, MPO in MPA/EGPA) generates circulating ANCA IgG
2. **Neutrophil activation:** ANCA binds to PR3/MPO on neutrophil surface (or in cytoplasm)
3. **Complement activation:** IgG-ANCA-antigen complexes activate classical complement cascade
4. **Neutrophil degranulation:** Activated neutrophils release proteases, ROS ☐ endothelial damage
5. **Vasculitis cascade:** Endothelial injury ☐ vessel wall necrosis, fibrinoid necrosis, crescents

Key point: Pauci-immune pattern means **minimal Ig and complement deposits on immunofluorescence** (despite circulating ANCA); deposits are scanty because most damage is from cellular mechanisms (ANCA-activated neutrophils), not immune complexes.

Diagnostic Approach to AAV

Step 1: Clinical Suspicion Red flags for AAV: - **Rapidly progressive glomerulonephritis** (rising Cr over days–weeks) - **Upper respiratory involvement + glomerulonephritis** (GPA) - **Pulmonary hemorrhage + glomerulonephritis** (GPA or MPA) - **ANCA positivity** on screening - **Necrotizing glomerulonephritis on biopsy** (any site)

Step 2: Serologic Testing A. ANCA Testing:

Test	Interpretation	Associated Disease
c-ANCA (cytoplasmic)	Coarse, cytoplasmic IgG staining	PR3-ANCA; 90% GPA
p-ANCA (perinuclear)	Perinuclear/nuclear rim staining	MPO-ANCA; MPA, EGPA
PR3-ANCA (ELISA)	Specific for proteinase 3 antigen	GPA (>95% specific)

Test	Interpretation	Associated Disease
MPO-ANCA (ELISA)	Specific for myeloperoxidase antigen	MPA, EGPA, atypical AAV
ANCA-negative	No c-ANCA or p-ANCA detected	5–10% AAV; seronegative EGPA, atypical cases

Diagnostic algorithm:

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Suspected AAV (RPGN, upper resp, pulm hemorrhage)
  ↓
ANCA testing (by immunofluorescence + ELISA)
  ├─ c-ANCA/PR3 positive → GPA likely
  ├─ p-ANCA/MPO positive → MPA or EGPA (differentiate by clinical context)
  ├─ p-ANCA/ANCA-negative → Seronegative AAV or alternative diagnosis
  └─ If ANCA positive → Kidney biopsy to confirm
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B. Supplementary Tests:

Test	Purpose	Expected Finding
CBC	Check for systemic involvement	Eosinophilia (EGPA), anemia of chronic disease
CMP	Assess renal function, electrolytes	Elevated Cr (RPGN), hyperkalemia (if oliguric)
Urinalysis	Assess glomerulonephritis	RBC casts, dysmorphic RBCs, proteinuria
Protein/Creatinine Ratio	Quantify proteinuria	Usually <3.5 g/day (vs. >3.5 in immune complex GN)
ANA, anti-GBM	Rule out mimics	Negative in AAV (positive suggests SLE, Goodpasture)
Chest X-ray	Pulmonary involvement	Nodules (GPA), infiltrates (MPA), ground-glass (pulm hemorrhage)

Step 3: Kidney Biopsy **Indication:** Confirm diagnosis if ANCA positive and RPGN clinically suspected.

Light microscopy: - **Necrotizing glomerulonephritis:** Fibrinoid necrosis of capillary walls, crescent formation (cellular, fibrocellular, or fibrous) - **Segmental necrosis:** Some glomeruli involved; others normal or sclerotic - **Interstitial inflammation:** T cells, macrophages, some eosinophils (especially EGPA)

Immunofluorescence: - **Pauci-immune pattern:** Negative or minimal staining for IgG, IgA, IgM, C3, C4 - This is the hallmark of AAV (distinguishes from immune complex disease with heavy deposits)

Electron microscopy: - **Sparse or absent immune deposits** (pauci-immune) - Endothelial damage, RBCs in urinary space

ANCA-negative cases: - If clinical suspicion high but ANCA negative, biopsy confirmation essential

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III. Anti-GBM Disease (Goodpasture Syndrome)

Definition and Epidemiology

Anti-GBM disease is a **rare, autoimmune, small-vessel vasculitis** characterized by: - **Circulating anti-glomerular basement membrane (anti-GBM) antibodies** (IgG) - **Linear IgG deposition** along the basement membrane of kidneys (and sometimes lungs, skin) - **Rapidly progressive glomerulonephritis**

Prevalence: Rare; <1% of glomerulonephritis cases; ~1 per 10 million per year

Age of onset: Young adults (20–30 years); can occur at any age

Male predominance: Slight (M:F = 1.2:1)

Forms of Anti-GBM Disease

1. Anti-GBM Nephritis Alone (Renal Limited)

- **Isolated glomerulonephritis** without pulmonary hemorrhage
- ~50% of anti-GBM cases
- Rapid progression to ESRD if untreated

2. Goodpasture Syndrome (Pulmonary-Renal)

- **Glomerulonephritis + pulmonary hemorrhage**
- ~50% of anti-GBM cases
- **Classic presentation:** Young patient with hemoptysis + hematuria
- **Often associated with smoking** (may increase risk or unmask disease)
- **Mortality higher** without prompt treatment

Pathophysiology

Anti-GBM Antibody and Basement Membrane Attack:

1. **Immune response to NC1 domain of alpha-3 chain of collagen IV** (major component of GBM)
2. **IgG anti-GBM antibodies** bind to epitope on GBM and alveolar basement membrane
3. **Linear IgG deposition** along full length of GBM (pathognomonic pattern)
4. **Complement activation:** IgG-antigen complexes fix classical complement (C1q)
5. **Membrane attack complex (C5b-9):** Forms in basement membrane; creates pores, causes cell lysis
6. **Neutrophil infiltration:** Complement-driven recruitment of neutrophils ☐ additional injury
7. **Basement membrane rupture:** From acute inflammation; creates crescents (fibrin, cells)

Result: Rapidly progressive glomerulonephritis with crescent formation; can cause ESRD within days to weeks if untreated.

Clinical Presentation

Renal manifestations: - **Hematuria:** Often visible; dark/cola-colored urine - **Dysmorphic RBCs and RBC casts:** Glomerular bleeding - **Proteinuria:** Usually mild (<1–2 g/day, less than immune complex GN) - **Rapidly rising creatinine:** RPGN pattern; Cr may double in days - **Hypertension:** Common; from fluid retention and HTN cascade

Pulmonary manifestations (Goodpasture): - **Hemoptysis:** Coughing up blood (can be bloody sputum or massive bleeding) - **Dyspnea:** From pulmonary hemorrhage and pulmonary edema - **Chest pain:** From pleural involvement - **CXR findings:** "Bat-wing" or diffuse infiltrates (alveolar hemorrhage) - **Hypoxemia:** From V/Q mismatch (blood in alveoli)

Systemic manifestations: - **Constitutional:** Fever, malaise, fatigue (from acute inflammation) - **Joint pain:** Arthralgia (less common than vasculitis) - **Skin involvement:** Rare; maculopapular rash - **Notably ABSENT:** Upper respiratory involvement (unlike GPA), granulomas, eosinophilia

Diagnostic Approach to Anti-GBM Disease

Step 1: Clinical Suspicion Red flags: - **Hemoptysis + hematuria** (pulmonary-renal syndrome) - **Rapidly progressive GN** in young patient - **Linear IgG pattern on kidney biopsy** (pathognomonic) - **Anti-GBM serology positive**

Step 2: Serologic Testing

Test	Method	Interpretation
Anti-GBM ELISA	Blood serum ELISA for anti-GBM IgG	Positive in >90% of anti-GBM disease
Anti-GBM direct assay	Newer method targeting specific NC1 domain	Even more specific
ANCA testing	c-ANCA/p-ANCA	Should be NEGATIVE in pure anti-GBM (if positive, consider double-seronegative AAV or overlap)
Anti-GBM on kidney biopsy	Immunofluorescence	**Linear IgG** along GBM (diagnostic)

Diagnostic algorithm:

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Suspected anti-GBM (pulmonary-renal, RPGN)
  ↓
Anti-GBM serology (ELISA)
  ├─ Anti-GBM positive → Very likely anti-GBM disease
  ├─ Anti-GBM negative → Kidney biopsy needed
  └─ Kidney biopsy confirms (linear IgG pattern)
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Step 3: Kidney Biopsy **Light microscopy:** - **Necrotizing glomerulonephritis:** Cellular, fibrocellular, or fibrous crescents - **Segmental necrosis:** GBM breaks occur - **RBCs in urinary space**

Immunofluorescence (diagnostic): - **Linear IgG deposition** along the entire basement membrane (glomerular and sometimes tubular BM) - **Other Ig/complement:** Minimal or negative (pauci-immune pattern) - **This pattern is pathognomonic** for anti-GBM disease

Electron microscopy: - Glomerular basement membrane disruption, electron density changes - Sparse or absent electron-dense deposits (pauci-immune pattern)

Lung biopsy (if pulmonary involvement, rarely needed for diagnosis): - Alveolar hemorrhage - **Linear IgG along alveolar basement membrane** (same epitope as glomerular)

IV. Complement-Mediated Glomerular Diseases: C3 Glomerulopathy

Definition and Classification

C3 glomerulopathy (C3GN) is a **group of glomerular diseases** characterized by: - **Predominant C3 deposition** on immunofluorescence (without significant Ig co-deposition) - **Dysregulation of alternative complement pathway** - **Progressive glomerulonephritis** (hematuria, proteinuria, declining GFR)

Previously classified as: MPGN (membranoproliferative GN) Type II or III

Current classification (2013 update): C3 glomerulopathy is now **distinguished from immune complex MPGN** because pathophysiology is complement-driven, not Ig-driven.

Subtypes:

Subtype	Characteristics	Pathophysiology
C3 Glomerulonephritis (C3GN)	Proliferative GN, C3 dominant	Dysregulated alternative pathway activation in glomeruli
Dense Deposit Disease (DDD)	Formerly MPGN-IC (intramembranous); "ribbon-like" dense deposits	Factor H deficiency or Factor H autoantibodies; severe alternative pathway dysregulation
Post-Infectious GN	Post-streptococcal, post-other infections	Immune complexes + alternative pathway activation (transitional pattern)
MPGN-Type I with C3 Codominance	Classic MPGN-I with prominent C3	Immune complexes + complement activation

Focus: C3GN and DDD (acquired vs. genetic factors).

Pathophysiology of C3 Glomerulopathy

Complement Cascade Overview Classical Pathway (IgG/IgM ☐ C1q): 1. IgG/IgM binds antigen 2. C1q (component of C1 complex) binds to Fc region of Ig 3. C1r, C1s activated 4. C2, C4 activated 5. C3 convertase (C4b2a) formed 6. C3 ☐ C3a + C3b

Lectin Pathway (MBL ☐ MASP): 1. Mannose-binding lectin (MBL) binds to carbohydrate on pathogen or cell surface 2. MASP-1, MASP-2 activated (similar to C1r/C1s) 3. C2, C4 activated 4. C3 convertase formed (same as classical: C4b2a)

Alternative Pathway (constitutive, "amplification loop"): 1. **Constant low-level activation:** C3 spontaneously hydrolyzes (C3 hydrolysis) ☐ C3a + C3b 2. **Feedback amplification:** - C3b binds Factor B (proenzyme) - Factor D cleaves B ☐ Ba + Bb - C3b + Bb = C3 convertase (alternative pathway) - Each C3b recruits more Factor B ☐ Bb ☐ creates more C3 convertase 3. **Regulation:** Factor H (serum protein) + Complement Receptor 1 (CR1) inactivate C3b 4. **In dysregulation:** Loss of Factor H (genetic or autoantibodies) ☐ uncontrolled C3 activation

Terminal Pathway (All three feed in): - C3b ☐ C5 convertase formed - C5 ☐ C5a (anaphylatoxin) + C5b - C5b + C6 + C7 + C8 + C9 = Membrane Attack Complex (MAC, C5b-9) - MAC inserts in membrane ☐ cell lysis, inflammatory damage

In C3 Glomerulopathy Problem: Alternative Pathway Dysregulation

Mechanisms:

1. **Genetic mutations (hereditary C3GN):**
    - **Factor H mutations** (most common, ~30% of C3GN): Loss-of-function ☐ impaired C3b inactivation
    - **Factor B gain-of-function mutations** (10–15%): Creates hyperactive C3 convertase
    - **C3 gain-of-function mutations** (10%): C3 resists Factor H inactivation
    - **MCP (CD46) mutations** (5%): Membrane-bound regulator defective
    - **CFHR1/CFHR3 deletions** (10%): Loss of negative regulator
2. **Acquired mechanisms (sporadic C3GN):**
    - **Factor H autoantibodies** (CFHR5-Factor H hybrid antibodies): Bind to Factor H ☐ block C3b inactivation
    - **C3 nephritic factor (C3NeF):** IgG autoantibody stabilizing C3 convertase (prevents degradation)
    - **Post-infectious:** Immune complexes activate classical pathway ☐ amplification loop ☐ alternative pathway contribution

Result of dysregulation: - **Uncontrolled C3 deposition** in glomeruli - **C3b-rich inflammatory environment** ☐ neutrophil recruitment, endothelial damage, crescent formation - **Minimal or absent Ig deposition** (because pathway is complement-driven, not immune complex-driven)

C3 Glomerulonephritis (C3GN)

Definition: C3GN is a glomerular disease with **isolated or dominant C3 deposits without significant Ig** on immunofluorescence.

Pathology: - **Light microscopy:** Proliferative glomerulonephritis - Endocapillary or membranoproliferative pattern - Cellularity with hypercellularity (endocapillary expansion) - Possible crescent formation (crescentic variant) - **Immunofluorescence: C3-dominant or isolated C3 deposits** - Granular pattern in capillary wall and mesangium - **Minimal or NO IgG, IgA, IgM** (distinguishes from immune complex disease) - Possible C1q, C4 (if classical pathway contribution) - **Electron microscopy:** - Electron-dense deposits in subendothelial space (in glomerular capillary wall) - Possible hump-like subepithelial deposits (post-infectious picture) - Possible organized dense material

Clinical presentation: - **Hematuria:** Microscopic or gross; RBC casts - **Proteinuria:** Mild to nephrotic range - **Hypertension:** Common; from glomerulonephritis - **Progressive renal insufficiency:** Decline in GFR over months to years - **Age:** Can occur at any age; both children and adults - **Course:** Variable; some progress to ESRD, others stable

Prognosis without treatment: - ~50% progress to ESRD within 10 years - Worse prognosis if: heavy proteinuria, crescents, Factor H mutations, Factor H autoantibodies

Dense Deposit Disease (DDD) — Formerly MPGN-IC Type II

Definition: DDD is a severe form of complement-mediated GN with **characteristic "ribbon-like" electron-dense intramembranous deposits** on electron microscopy.

Pathology: - **Light microscopy:** Membranoproliferative pattern - Increased mesangial cellularity - Capillary wall thickening (double contour/"tram-track") - Possible crescents (more severe) - **Immunofluorescence: C3-dominant** (often isolated C3, may have minimal Ig) - Granular pattern; more prominent than in C3GN typically - **Electron microscopy (diagnostic):** - **"Ribbon-like" or "organized," electron-dense deposits** - Located in intramembranous location (within the glomerular basement membrane) - Highly organized, often described as "organized" or "ribbon-like" appearance - **This appearance is DIAGNOSTIC for DDD** (formerly called MPGN-IC Type II)

Clinical features: - **More aggressive than C3GN:** Earlier progression to ESRD - **Genetic basis common:** Factor H mutations, Factor H autoantibodies, C3 mutations - **Post-infectious:** Can follow infection (post-streptococcal), though true DDD often has genetic basis - **Age:** Often in children/young adults; can occur at any age - **Prognosis:** ~50% ESRD within 5 years if untreated

Recurrence post-transplant: Very high recurrence rate (especially Factor H mutations); requires monitoring and preventive strategies.

V. Serologic Testing Algorithms and Complement Pattern Interpretation

Diagnostic Algorithm: Which Test First?

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Suspected Glomerulonephritis (hematuria, RBC casts, proteinuria, rising Cr)
  ↓
Urinalysis (hematuria + RBC casts confirm GN)
Serum Cr, BUN (assess renal function)
  ↓
Rapid Serologic Screening:
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  ├─ ANA (for lupus nephritis)
  ├─ ANCA (c-ANCA/PR3, p-ANCA/MPO for AAV)
  ├─ Anti-GBM (for anti-GBM disease)
  ├─ Anti-dsDNA, anti-Smith (if ANA positive, for lupus)
  ├─ Complement levels (C3, C4)
  ├─ Cryoglobulins (if appropriate)
  └─ ABO/Rh typing (if post-infectious suspected)
  ↓
Kidney biopsy (if diagnosis unclear from serology + clinical context)
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Serologic Pattern Interpretation

Finding	Interpretation	Likely Diagnoses
ANCA+ (c-ANCA/PR3)	Pauci-immune vasculitis, PR3-driven	GPA, ANCA-GN
ANCA+ (p-ANCA/MPO)	Pauci-immune vasculitis, MPO-driven	MPA, EGPA, MPO-ANCA GN
ANCA−, RPGN on biopsy, pauci-immune	Seronegative AAV or other pauci-immune	Seronegative AAV, atypical vasculitis, anti-GBM (if linear IgG)
Anti-GBM+, linear IgG on biopsy	Anti-GBM disease	Goodpasture syndrome or renal-limited anti-GBM
C3 dominant (low Ig) on biopsy	Complement dysregulation	C3GN, DDD, post-infectious GN
C1q+ on biopsy	Classical pathway activation	Immune complex disease (lupus, post-infectious, cryoglobulinemia)
ANA+, anti-dsDNA+	SLE	Lupus nephritis
C3□, C4□ (both low)	Immune complex activation (classical pathway)	Lupus, post-infectious GN, cryoglobulinemia
C3□, C4 normal	Alternative or lectin pathway	C3GN, post-infectious GN, MPGN-Type I (if IC)
IgA-dominant on biopsy	IgA deposits	IgA vasculitis (IgAN)

Complement Protein Interpretation

Normal levels: - C3: 90–180 mg/dL - C4: 10–40 mg/dL

Low C3 + Low C4: - **Classical pathway activated** (IgG/IgM immune complex formation) - **Diagnoses:** Lupus nephritis, post-streptococcal GN, cryoglobulinemia, MPGN-Type I (IC) - **Mechanism:** Immune complexes consume classical pathway components (C1q, C4, C2); C3 consumed as substrate

Low C3 + Normal C4: - **Alternative or lectin pathway activated** (or classical pathway but more selective C3 consumption) - **Diagnoses:** C3GN, DDD, post-infectious GN with alternative

pathway amplification - **Mechanism:** Alternative pathway (lacks C1q, C4) is dysregulated; C3 consumed; C4 spared

Normal C3 + Low C4: - **Selective C4 consumption** (unusual) - **Consider:** Early disease, activation via lectin pathway only, or laboratory artifact

Normal C3 + Normal C4: - **Complement not significantly activated** (or assays obtained late, after consumption resolved) - **Consider:** Early GN, IgA vasculitis (low complement uncommon), ANCA-associated vasculitis (pauci-immune, no significant complement deposition)

VI. Management of Vasculitis and ANCA-Associated Disease

Acute AAV (ANCA-Associated Vasculitis)

Induction Therapy (remission induction, first 3–6 months):

Standard regimen: 1. **High-dose corticosteroids:** - IV methylprednisolone 500–1000 mg daily × 3 days, then - Prednisone 1 mg/kg daily (max 80 mg), tapered over weeks–months 2. **Immunosuppression:** - **Cyclophosphamide (for severe/renal disease):** - Pulse IV cyclophosphamide 500–1000 mg/m² monthly × 3–6 months OR - Oral cyclophosphamide 2 mg/kg daily - Monitor CBC; adjust for myelosuppression - Mesna (uroprotective agent) to prevent hemorrhagic cystitis - **Rituximab (alternative, increasingly preferred):** - IV infusions 375 mg/m² weekly × 4 weeks OR - 1000 mg IV × 2 doses 2 weeks apart - Less myelosuppression; preferable in older patients, reproductive concerns 3. **Plasma exchange (for severe pulmonary hemorrhage, rapidly rising Cr, oliguria):** - Daily or alternate-day plasma exchange × 7–14 sessions - Goal: Remove ANCA, immune complexes, inflammatory mediators

Maintenance Therapy (remission maintenance, months 6–24+): - **Azathioprine 1.5–2 mg/kg daily** or - **Mycophenolate mofetil 1000–1500 mg BID** or - **Rituximab maintenance** (re-dosing every 6–12 months) - **Low-dose prednisone** (taper goal: 0.1–0.2 mg/kg by 3–4 months)

Adjunctive measures: - **Prophylactic antibiotics:** Trimethoprim-sulfamethoxazole (TMP-SMX) reduces relapse risk (probably via Pneumocystis prophylaxis or anti-Staphylococcus effect) - **Renal replacement therapy:** If oliguric/anuric ARF, initiate dialysis early (does not preclude recovery) - **Blood pressure control:** ACE-I/ARB for reno-protection - **Monitoring:** ANCA titers (relative), CBC, CMP, LFTs (monthly during induction; periodic during maintenance)

Prognosis of AAV with treatment: - **Remission rate:** 70–90% with current regimens - **Complete remission:** 50–70% achieve ANDA-negativity - **Relapse rate:** 20–50% within 5 years; managed with re-induction - **ESRD incidence:** 10–20% if creatinine >3 mg/dL at diagnosis; lower if early recognition and treatment

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Anti-GBM Disease

Urgent treatment required (can progress to dialysis-dependent ESRD in days):

Induction Therapy: 1. **Plasma exchange:** IMMEDIATE initiation - Daily plasma exchange × 10–14 sessions (or until anti-GBM serology negative) - **Goal:** Remove circulating anti-GBM

antibodies - **Urgent:** Should begin within hours of diagnosis (any delay □ progressive irreversible injury) 2. **Corticosteroids:** - IV methylprednisolone 500–1000 mg × 3 days, then - Prednisone 1 mg/kg daily, tapered over weeks–months 3. **Immunosuppression:** - **Cyclophosphamide 2 mg/kg daily OR** - **Rituximab** (increasingly used; may be superior to cyclophosphamide) - Goal: Suppress anti-GBM antibody production from B cells/plasma cells

Duration: - Continue plasma exchange until anti-GBM serology negative (usually 7–14 sessions) - Continue corticosteroids and immunosuppression × 3–6 months (similar to AAV) - Maintenance therapy: Azathioprine or mycophenolate for 12–24 months

Prognosis: - **If treated urgently:** Can prevent progression to ESRD in ~70% if Cr <3 mg/dL at diagnosis - **If creatinine >3 mg/dL or oliguric at diagnosis:** Only 10–20% recover renal function despite aggressive treatment - **Pulmonary hemorrhage:** Can be life-threatening; controlled with plasma exchange + steroids + immunosuppression - **Recurrence:** Rare (<5%) with adequate B-cell suppression

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C3 Glomerulopathy (C3GN and DDD)

Current management (Evidence evolving):

First-line (supportive care): - **ACE-I/ARB:** To reduce proteinuria and slow progression - **Blood pressure control:** Target <120/80 or lower if tolerated - **Statin:** Possible pleiotropic effects (anti-inflammatory) - **Prophylactic antibiotics (TMP-SMX):** May reduce proteinuria/progression (controversial)

If progressive (rising Cr, heavy proteinuria, crescents): - **Corticosteroids:** Pulse methylprednisolone or oral prednisone - **Immunosuppression (limited evidence):** - **Mycophenolate mofetil:** 1000–1500 mg BID (some benefit in case series) - **Cyclophosphamide:** If rapidly progressive - **Rituximab:** Early data suggest benefit in Factor H-associated disease - **Plasma exchange:** If severe/rapidly progressive (potential benefit in some cases)

Targeted therapy (emerging): - **Factor H (recombinant):** For Factor H deficiency (rare; experimental) - **Anti-C5 monoclonal (eculizumab, C5 inhibition):** Shows promise in Factor H-associated and Factor H autoantibody disease (some case series; larger trials ongoing) - **Factor D inhibitor:** Blocks alternative pathway activation (experimental) - **Factor B inhibitor:** Blocks C3 convertase formation (experimental)

Transplantation considerations: - **High recurrence rate:** Especially DDD and Factor H-associated disease - **Preventive measures:** Some centers use prophylactic plasma exchange, immunosuppression, or complement-inhibition post-transplant - **Outcome:** Recurrence does not necessarily preclude graft survival; monitoring and management can prevent total graft loss

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VII. Clinical Pearls

1. **AAV is pauci-immune:** Minimal Ig and complement deposits on immunofluorescence distinguish AAV from immune complex disease; damage is neutrophil-mediated (ANCA-driven).

2. **c-ANCA/PR3 = GPA; p-ANCA/MPO = MPA/EGPA:** But clinical context (upper respiratory, granulomas, cardiac) also critical for classification.
3. **Anti-GBM disease requires URGENT treatment:** Plasma exchange should begin within hours; delays lead to irreversible ESRD.
4. **Linear IgG on kidney biopsy is pathognomonic for anti-GBM disease:** This finding + pulmonary hemorrhage = Goodpasture syndrome (pulmonary-renal).
5. **C3 predominant (no Ig or minimal Ig) on biopsy suggests C3GN or DDD:** Complement-driven, not Ig-driven; search for Factor H mutations/autoantibodies if severe.
6. **Low C3 + low C4 = classical pathway activated** (immune complexes); low C3 + normal C4 = alternative pathway (C3GN).
7. **Post-infectious GN is the most common secondary RPGN** worldwide (especially post-streptococcal in children); immune complexes + alternative pathway amplification.
8. **ANCA-negative RPGN exists:** 5–10% of AAV are ANCA-negative; biopsy (showing pauci-immune necrotizing GN) confirms diagnosis.
9. **Seronegative EGPA (ANCA-negative EGPA) is an important diagnosis:** 40–60% of EGPA are ANCA-negative; clinical context (asthma, eosinophilia, vasculitis) is diagnostic.
10. **Cyclophosphamide and rituximab are equally effective for AAV induction:** Choice depends on age, side effect profile, fertility concerns; rituximab preferred in some centers.
11. **ANCA titers do NOT reliably predict relapse:** Rising ANCA during remission may not indicate imminent relapse; clinical judgment and ANCA-negative conversion as therapeutic goal.
12. **DDD has very high recurrence post-transplant:** Requires monitoring with graft biopsy; preventive strategies (plasma exchange, complement inhibition) used in some centers.

VIII. Practice Questions

Question 1: A 52-year-old man with productive cough, hemoptysis, and hematuria is found to have creatinine 3.8 mg/dL and urinalysis with dysmorphic RBCs and RBC casts. Chest X-ray shows bilateral infiltrates. c-ANCA/PR3 is positive. What is the most likely diagnosis?

A) Anti-GBM disease (Goodpasture syndrome)
B) Granulomatosis with polyangiitis (GPA)
C) Microscopic polyangiitis (MPA)
D) Lupus nephritis

Correct Answer: B Explanation: The combination of **upper respiratory involvement (sinusitis often precedes pulmonary disease)**, **pulmonary hemorrhage (hemoptysis, infiltrates)**, **rapidly progressive GN (high Cr with hematuria/casts)**, and **c-ANCA/PR3 positivity** is classic for GPA. While anti-GBM also presents with pulmonary-renal syndrome, c-ANCA/PR3 is negative in anti-GBM (it is anti-GBM ELISA positive). MPA typically does NOT

have upper respiratory involvement. Kidney biopsy would show necrotizing GN with granulomas (not just necrotizing, distinguishing from MPA).

Question 2: A 28-year-old woman with hemoptysis (bright red blood) and hematuria is found to have creatinine 2.2 mg/dL and anti-GBM ELISA positive. Chest X-ray shows bilateral alveolar infiltrates. She is NOT ANCA positive. What is the MOST important first step in management?

A) Start oral corticosteroids and plan kidney biopsy
B) IMMEDIATELY start plasma exchange daily; initiate steroids and cyclophosphamide
C) Start rituximab and monitor anti-GBM titers
D) Start hemodialysis (for oliguria/hyperkalemia management)

Correct Answer: B Explanation: **Anti-GBM disease with pulmonary-renal involvement (Goodpasture syndrome) is a renal emergency.** Plasma exchange must be initiated **IMMEDIATELY** (within hours of diagnosis) to remove circulating anti-GBM antibodies before they cause irreversible basement membrane destruction. Delays in initiating plasma exchange correlate with progression to dialysis-dependent ESRD. Corticosteroids and cyclophosphamide/rituximab are initiated concurrently with plasma exchange to suppress further antibody production. Kidney biopsy can be done after stabilization (though clinical + serology typically diagnostic).

Question 3: A kidney biopsy shows necrotizing glomerulonephritis with a **pauci-immune pattern on immunofluorescence** (minimal IgG, IgA, IgM). c-ANCA and p-ANCA are both negative; anti-GBM is negative. What is the most likely diagnosis?

A) IgA vasculitis (IgAN)
B) Seronegative ANCA-associated vasculitis
C) Post-infectious glomerulonephritis
D) Lupus nephritis

Correct Answer: B Explanation: The **pauci-immune pattern on biopsy** is the hallmark of AAV, regardless of serology. About 5–10% of AAV cases are ANCA-negative ("seronegative AAV"). This diagnosis requires the combination of: (1) necrotizing GN on biopsy, (2) pauci-immune pattern, and (3) negative ANCA. IgA vasculitis would show IgA-dominant deposits, not pauci-immune. Post-infectious GN would typically have immune complex deposition and possible complement, not pure pauci-immune. Lupus would have multi-Ig deposits and positive ANA.

IX. References

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See Also

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- Nephritic and Nephrotic Syndromes
- Lupus Nephritis
- IgA Nephropathy
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End of Handout

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