

RPGN Diagnostic Algorithm

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Overview

Rapidly progressive glomerulonephritis (RPGN) is a clinical-pathologic syndrome characterized by rapid loss of glomerular filtration rate (GFR) (50% decline over days to 3 months) accompanied by crescent formation on renal biopsy [1]. RPGN is a renal emergency requiring prompt diagnosis and immunosuppression to preserve kidney function. This guide provides a stepwise diagnostic and treatment approach based on immunofluorescence (IF) and serologic findings.

Key Clinical Pearl

“RPGN is a medical emergency. If clinical suspicion is high (rapid SCr rise + active urinary sediment + absence of other explanations), initiate empiric immunosuppression BEFORE biopsy results return; waiting may result in irreversible renal failure.” The three types are distinguished by IF pattern on biopsy, but serologic workup can guide presumptive therapy.

Part 1: RPGN Definition and Classification

RPGN Clinicopathologic Definition

Clinical Criteria: - Rapid GFR decline (SCr rises $\geq 50\%$ or Cr clearance falls $\geq 50\%$ over days to 3 months) - Active urinary sediment (dysmorphic RBCs, RBC casts, proteinuria) - Absence of non-glomerular causes (prerenal, postrenal, ATN)

Pathologic Criteria: - **Crescent formation** ($>50\%$ of glomeruli involved in RPGN; 10–50% = “crescentic GN”) - Light microscopy (LM) shows fibrocellular or fibrinoid crescents with glomerular necrosis - Immunofluorescence (IF) determines type (see below)

Three Types of RPGN (IF-Based Classification)

Type	IF Pattern	Serology	Frequency	Prognosis
Type I: Anti-GBM	Linear IgG + C3 along GBM	Anti-GBM+ serum antibodies	10–15%	Poor if Cr >4 at presentation
Type II: Immune Complex (IC)	Granular IgG ± IgA ± IgM + C3	Varies (ANA+, anti-dsDNA, ASO titer, etc.)	20–30%	Depends on underlying disease
Type III: Pauci-Immune (ANCA)	Pauci-immune (minimal IF) ± ANCA on immunoelectron microscopy	ANCA+ (c-ANCA/PR3 or p-ANCA/MPO) in 90%; ANCA-negative in 10%	50–60%	Best if treated early; Cr >4 at presentation = poor

Key Distinction: “Crescent” vs “RPGN” Terminology

- **RPGN** = clinical syndrome of rapid GFR decline + biopsy findings (crescent formation)
- **Crescentic GN** = pathologic finding of crescent without necessarily rapid presentation
- **Not all crescents = RPGN** (e.g., IgA nephropathy with 10% crescents but stable Cr = not RPGN)

Part 2: Clinical Presentation and Initial Workup

Presenting Features of RPGN

Systemic symptoms (40–60%): - Malaise, fever, weight loss - Arthralgia, myalgia (especially in ANCA-associated)

Renal symptoms: - Hematuria (tea-colored or smoky urine; RBC casts on UA) - Oliguria or anuria (if severe) - Rapid rise in Cr over days/weeks (accelerated from baseline)

Pulmonary hemorrhage (10–15% of RPGN): - Dyspnea, hemoptysis - Bilateral alveolar infiltrates on CXR - Diffusion capacity reduced (DLCO↓); A-a gradient widened - Associated with Type I (anti-GBM; Goodpasture syndrome) or Type III (ANCA; GPA with pulmonary involvement)

Systemic vasculitis features (if ANCA-associated): - Palpable purpura (legs, buttocks) - Sinusitis, nasal ulcers (GPA) - Polyarthritides, constitutional symptoms

Urgent Baseline Laboratory Assessment

Renal function & urinalysis: - SCr, BUN, GFR (estimate baseline if not known) - Urinalysis: RBC casts (pathognomonic), dysmorphic RBCs, granular casts, proteinuria

Electrolytes & metabolic: - Sodium, K, Cl, HCO₃, phosphate (assess AKI severity) - Ca (hypocalcemia suggests rhabdomyolysis or sepsis, not RPGN)

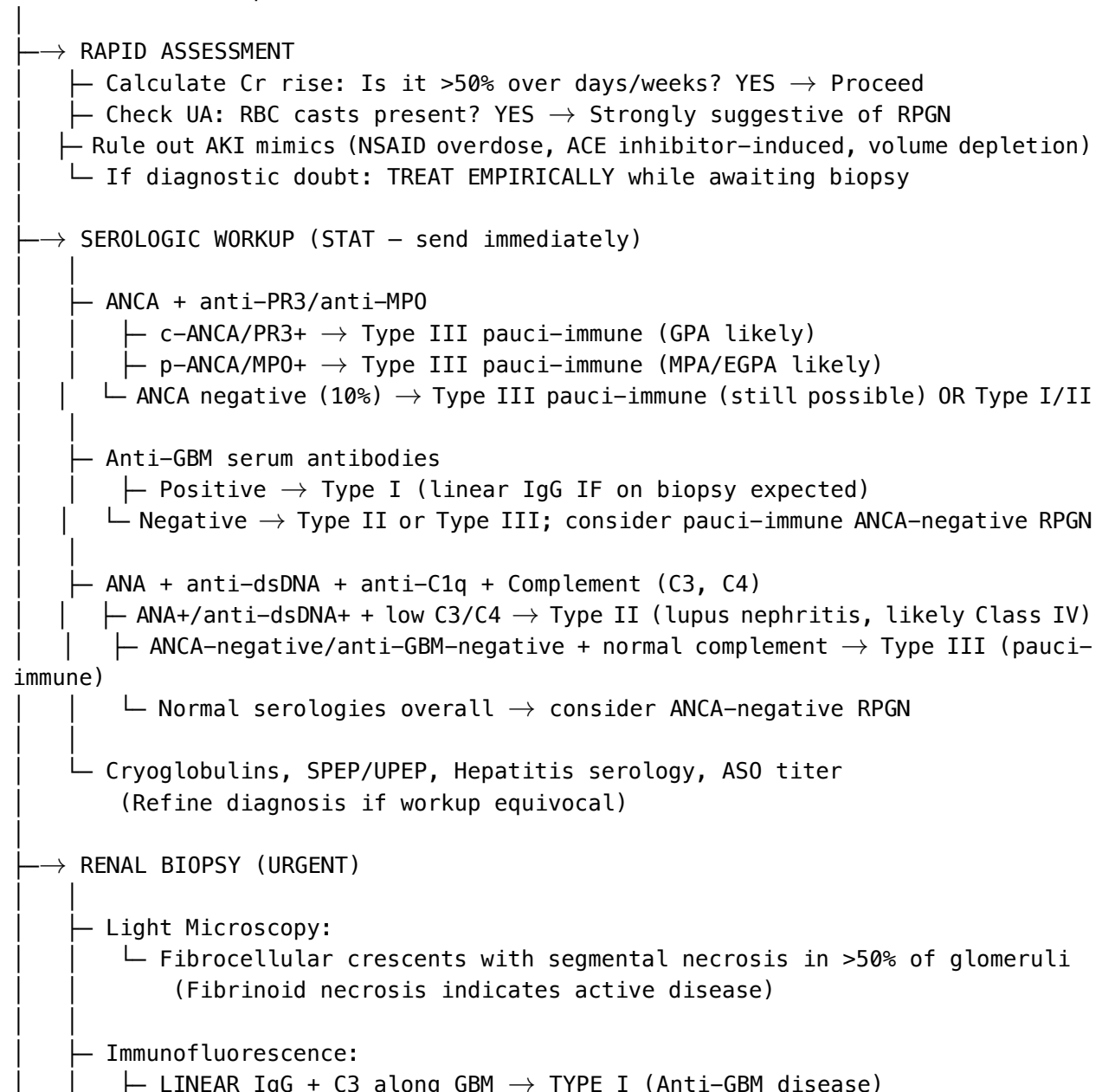
Coagulation & anemia: - PT/INR, aPTT (assess bleeding risk if biopsy planned) - CBC (anemia from hematuria; thrombocytopenia rare in RPGN)

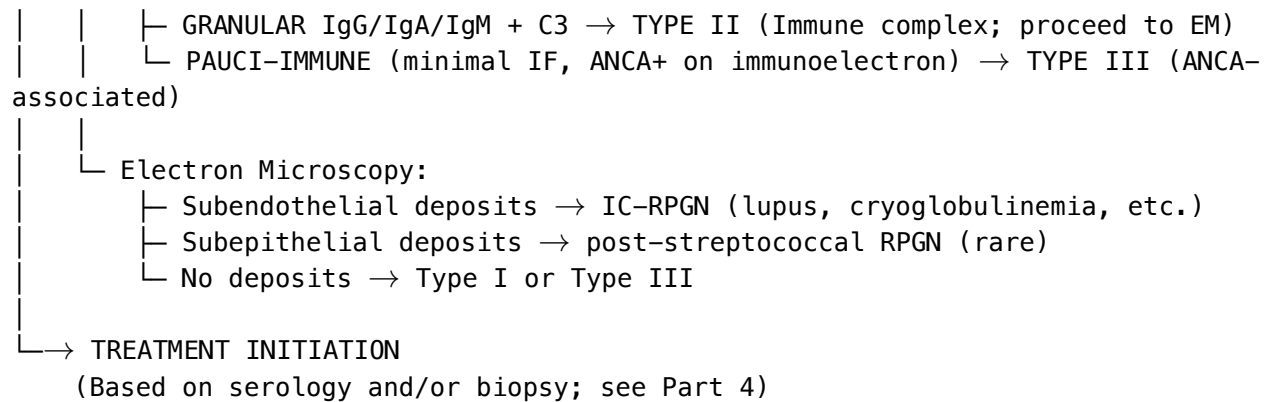
Serologic panel (send immediately; do NOT delay for biopsy): - ANCA + anti-PR3 + anti-MPO (ANCA-associated vasculitis) - Anti-GBM (Type I) - ANA + anti-dsDNA + anti-C1q (lupus) - Complement: C3, C4, CH50 - Cryoglobulins, SPEP/UPEP (monoclonal protein) - Blood cultures (if fever; exclude infection-associated GN) - Hepatitis serology (HBV, HCV; associated with vasculitis) - ASO titer, anti-hyaluronidase (post-streptococcal)

Imaging: - Chest X-ray (evaluate for pulmonary hemorrhage) - Renal ultrasound (assess kidney size, echogenicity, rule out obstruction)

Part 3: RPGN Diagnostic Algorithm

SUSPECTED RPGN (rapid Cr rise + active sediment)





Part 4: Serologic Interpretation for Immediate Therapy Guidance

If ANCA+ (c-ANCA/PR3 or p-ANCA/MPO): Type III Presumptive Diagnosis

Presumed diagnosis: ANCA-associated vasculitis (AAV) with RPGN.

ANCA subtypes: - **c-ANCA/anti-PR3 (60% of AAV-RPGN):** Granulomatosis with polyangiitis (GPA) - Upper respiratory involvement common (sinusitis, nasal ulcers, subglottic stenosis) - Lower respiratory involvement (pulmonary nodules, infiltrates, hemorrhage) - **p-ANCA/anti-MPO (40% of AAV-RPGN):** Microscopic polyangiitis (MPA) or eosinophilia-associated - Pulmonary hemorrhage more common - Skin/GI involvement frequent - Pulmonary granulomas rare

Immediate therapy (induction): - High-dose corticosteroids (methylprednisolone 500–1000 mg IV daily × 3 days, then oral prednisone taper) - **Immunosuppression induction:** Rituximab 375 mg/m² IV weekly × 4 weeks (preferred) OR cyclophosphamide 15 mg/kg IV monthly × 3–6 months - If pulmonary hemorrhage: Add plasmapheresis (controversial; consider if hemoptysis, diffuse alveolar hemorrhage with Hgb drop, or anti-GBM coexistence)

Maintenance (18–24 months): - Rituximab 500 mg IV at 6 months, then every 6–9 months × 18 months - OR azathioprine 1–2 mg/kg/day + low-dose prednisone

If Anti-GBM+: Type I Presumptive Diagnosis

Presumed diagnosis: Anti-glomerular basement membrane (anti-GBM) disease ± pulmonary hemorrhage (Goodpasture syndrome).

Clinical pearl: Anti-GBM disease is rare but often fulminant; pulmonary hemorrhage in 40–60%; dual-positive (anti-GBM + ANCA) in 10% (worse prognosis).

Urgent therapy (EMERGENCY induction): - **Plasmapheresis:** 50 mL/kg/day × 7–14 days (remove circulating anti-GBM antibodies IMMEDIATELY) - Continue daily until serum anti-GBM titer negative - Reduces morbidity/mortality significantly if initiated early - **High-dose steroids + cyclophosphamide:** Methylprednisolone 500–1000 mg IV daily × 3 days, then oral prednisone; cyclophosphamide 2 mg/kg/day (or 15 mg/kg IV monthly) - Continue until anti-GBM serology persistently negative

Prognosis: Creatinine >4.0 mg/dL at presentation = 80% progress to ESRD; Cr <3.0 with early plasmapheresis = 50–70% renal recovery.

If ANA+/Anti-dsDNA+/Low C3: Type II Presumptive Diagnosis

Presumed diagnosis: Lupus nephritis (Class III focal or Class IV diffuse crescentic).

Immediate therapy (induction): - High-dose corticosteroids (methylprednisolone 500 mg IV daily × 3 days, then oral prednisone) - Immunosuppression induction: **Mycophenolate mofetil (MMF) 2–3 g/day OR cyclophosphamide 500 mg IV monthly × 3–6 months** (cyclophosphamide preferred if Class IV with crescents)

Maintenance: - Azathioprine 1–2 mg/kg/day OR MMF 2 g/day + low-dose prednisone - Hydroxychloroquine 200–400 mg/day (retinopathy monitoring)

Specific for RPGN presentation: Consider plasmapheresis if severe (Cr >4 or oliguria) or double-seronegative (<50% IgG deposition on biopsy).

If ANCA-Negative, Anti-GBM-Negative: Type III (ANCA-Negative) Presumptive Diagnosis

Presumed diagnosis: ANCA-negative pauci-immune RPGN (10% of RPGN; poor prognosis).

Challenge: Serologies negative, but biopsy pauci-immune with crescents. Diagnosis confirmed only on biopsy.

Treat identically to ANCA-positive RPGN: - High-dose steroids + induction immunosuppression (rituximab or cyclophosphamide) - Outcomes: ANCA-negative patients have higher progression rates to ESRD (50–70% vs 40% in ANCA+)

Special consideration: May harbor complement-mediated RPGN or rare glomerulonephritis types; if no response to standard therapy, consider repeat biopsy or genetic testing (C3, CFH, CFHR mutations).

If Serologies Largely Negative: Atypical RPGN Types

Consider: 1. **Immune-complex RPGN without SLE:** Cryoglobulinemia (HCV+), post-streptococcal, drug-induced (propylthiouracil, hydralazine, levamisole) 2. **Monoclonal immunoglobulin-associated RPGN:** SPEP/UPEP shows M-spike; free light chain assay elevated 3. **Atypical complement-mediated RPGN:** Genetic mutations (CFH, CFI, C3); may respond poorly to standard therapy 4. **Infection-associated RPGN:** Endocarditis, HBV, HIV; treat underlying infection ± brief immunosuppression

Action: Obtain biopsy urgently; interpret EM findings carefully.

Part 5: Timeline and Treatment Decisions

Presentation to Therapy Initiation (Hours to Days)

Time	Action
Hour 0–2	Recognize RPGN (rapid Cr + active sediment); STAT serologic workup

Time	Action
Hour 2–6	Renal biopsy scheduled (urgent); imaging (CXR, renal ultrasound)
Hour 6–24	Biopsy performed $\pm$ preliminary LM/IF results available
Day 1–2	Full biopsy interpretation available (LM, IF, EM); begin induction therapy if RPGN confirmed
Day 2–7	Do NOT wait for biopsy if high clinical suspicion; empiric therapy justified

Risk of delay: Each week of untreated RPGN increases risk of permanent renal failure. A patient with Cr rising to 4.0 who waits 2 weeks for treatment is likely to progress to dialysis dependence.

Part 6: Special Clinical Scenarios

Dual-Positive Disease (ANCA+ AND Anti-GBM+)

Frequency: 5–10% of RPGN patients (mixed Type I/Type III).

Serologic clue: Both ANCA+ (usually p-ANCA/MPO) AND anti-GBM+ on same serum sample.

Prognosis: Worse than either disease alone; higher progression to ESRD.

Treatment: - Aggressive induction: Plasmapheresis (for anti-GBM) + high-dose steroids + cyclophosphamide - Continue until BOTH ANCA and anti-GBM titers negative

ANCA-Negative Pauci-Immune RPGN with Poor Response

Challenge: ANCA-negative RPGN treated with standard therapy (steroids + rituximab/cyclophosphamide) but no improvement in Cr; worsening renal function despite immunosuppression.

Diagnostic considerations: 1. **Complement-mediated RPGN:** C3GN; Factor H deficiency; C3 nephritic factor; genetic mutations 2. **Double-seronegative lupus nephritis:** Very rare; diagnosis of exclusion; confirm with kidney biopsy EM showing subendothelial deposits 3. **Anti-phospholipase A2 receptor (PLA2R) membranous nephropathy with crescent:** Rare; IF shows IgG + C3 in granular pattern but with subepithelial deposits on EM

Next steps: - Repeat kidney biopsy if diagnosis remains unclear - Genetic testing (CFH, CFI, C3) if atypical complement-mediated RPGN suspected - Complement-blocking therapies: Consider C5a complement inhibitor (iptacopan), C3 complement inhibitor (pegcetacoplan) in research settings

RPGN in Pregnancy

Challenge: Rapid GFR decline in pregnant/postpartum woman; RPGN diagnosis complicated by eclampsia/HELLP syndrome mimicry.

Key distinguishing features: - **RPGN:** RBC casts on UA (preeclampsia typically has proteinuria without casts); ANCA/anti-GBM positive - **Preeclampsia:** Hypertension, proteinuria, thrombocytopenia, elevated LFTs; no RBC casts; serologies negative

Treatment: - If RPGN confirmed: Corticosteroids + induction therapy (rituximab preferred over cyclophosphamide in pregnancy; teratogenic risk) - If timing allows: Delay induction therapy until post-partum (except if severe/life-threatening RPGN)

Part 7: Remission and Relapse Monitoring

Definitions

Complete remission: Renal function stabilization ($\text{Cr} < 1.5 \times$ baseline) + urinary sediment normalization (no RBC casts, < 5 RBC/hpf) + absence of systemic vasculitis.

Relapse: New-onset hematuria, RBC casts, or rising Cr in remission (common in ANCA-associated; 50% at 5 years).

Maintenance Monitoring (Post-Induction)

Parameter	Frequency	Threshold for Action
Serum creatinine	Monthly $\times$ 3 months, then 3-monthly	Rise $> 20\%$ suggests relapse
Urinary sediment	Monthly $\times$ 3 months, then 3-monthly	Appearance of RBC casts $\rightarrow$ relapse
ANCA titers	3-monthly in first year, then 6-monthly	Rising titer predicts relapse (predictive in 50% of cases)
CBC	6-monthly (if on azathioprine/MMF)	Monitor for cytopenias; adjust dose if Hgb < 10 or WBC < 3500
Transaminases	6-monthly (if on azathioprine/MMF)	Monitor for hepatotoxicity

Relapse Management

If rising ANCA titer but stable renal function and UA: - Intensify monitoring; consider pulse corticosteroids or rituximab booster (if > 1 year since last dose)

If new-onset hematuria/RBC casts + rising Cr: - Treat aggressively with rituximab booster or cyclophosphamide pulse - Rule out alternative diagnoses (infection, drug toxicity, secondary GN)

Part 8: Key Warnings

Warning 1: Never Assume “Overlap” Without Biopsy

A patient with both clinical ANCA-associated vasculitis AND a positive anti-GBM test may have true dual-positive disease (5–10% of RPGN) OR may have one disease with an incidental antibody. **Biopsy is essential** to determine IF pattern (linear vs pauci-immune) and guide therapy.

Warning 2: Pulmonary Hemorrhage Mandates Aggressive Therapy

Hemoptysis + alveolar infiltrates + anemia in a patient with RPGN = **Goodpasture syndrome or GPA with pulmonary hemorrhage**. This mandates: - Plasmapheresis (if anti-GBM or if type uncertain) - High-dose immunosuppression - ICU-level monitoring (airway protection if massive hemorrhage)

Failure to treat aggressively = rapid demise; ARDS from pulmonary hemorrhage is a leading cause of death in RPGN.

Warning 3: Cyclophosphamide Toxicity

Long-term cyclophosphamide (>6 months of pulse therapy) increases risk of: - **Hemorrhagic cystitis**: Monitor UAs; ensure aggressive hydration - **Malignancy**: Bladder cancer, lymphoma (5–10% at 10 years) - **Infection**: Opportunistic (PCP, CMV) from prolonged immunosuppression

Mitigation: Switch to maintenance azathioprine/MMF after induction; mesna in high-risk cyclophosphamide regimens; PCP prophylaxis if CD4 <200.

Warning 4: ANCA-Negative RPGN Has Worse Prognosis

10% of RPGN cases are ANCA-negative pauci-immune. These patients have: - Slower initial response to therapy (delayed Cr improvement) - Higher rates of ESRD progression (50–70% vs 40% in ANCA-positive) - Need for longer, more intensive induction therapy

Implication: Do not de-escalate therapy based on ANCA negativity; treat aggressively.

Related Resources

- ← Back to RPGN Hub
- ← Back to Glomerular Diseases Hub
- ← Back to Nephrology Hub
- Back to Medical Education Dashboard

References

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- [2] McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease. *Clin J Am Soc Nephrol*. 2017;12:1162–1172. [PubMed](#)
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- [4] Lionaki S, Blyth ER, Hogan SL, et al. Predictors of renal outcome and extrarenal manifestations in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. *Semin Nephrol*. 2014;34:349–361. [PubMed](#)

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