# Glomerular Disease Diagnostic Algorithm

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## Glomerular Disease Diagnostic Algorithm

### Overview

Glomerulonephritis (GN) is the leading cause of end-stage renal disease worldwide. Diagnosis requires systematic integration of clinical presentation (nephrotic vs nephritic spectrum), serologic markers (complement, autoantibodies, ANCA), and renal biopsy with light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM) findings [1]. This guide provides a flowchart-friendly diagnostic approach for rapid and accurate GN classification.

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### Key Clinical Pearl

**"The serologic workup MUST be sent BEFORE biopsy, and biopsy is mandatory for definitive diagnosis of GN unless clinical context is absolutely certain (e.g., IgA nephropathy in a 25-year-old with isolated hematuria and normal renal function)."** Serologies narrow the differential; biopsy confirms.

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### Part 1: Nephrotic vs Nephritic Spectrum

#### Nephrotic Syndrome

**Definition:** Proteinuria $\geq$3.5 g/day, hypoalbuminemia (<3.5 g/dL), hyperlipidemia, edema (from volume expansion).

**Pathophysiology:** Large molecular weight losses (immunoglobulins, albumin, complement factors) due to glomerular permeability increase.

**Clinical Features:** - Proteinuria dominant (often >10 g/day) - Hematuria mild or absent (dysmorphic RBCs may be present) - Hypertension: mild (20–30% of patients) - Renal function: usually preserved at presentation (unless FSGS, membranous) - Edema: peripheral, periorbital (from severe hypoalbuminemia) - Hypercoagulability: VTE risk from loss of anticoagulants (proteins C, S, antithrombin)

**BUN:Cr ratio:** Normal (10:1) because tubular function preserved.

**Major Nephrotic Diseases:** - Membranous nephropathy (MN) — 40% of nephrotic GN in adults - Minimal change disease (MCD) — 40% in children, 10% in adults - Focal segmental glomerulosclerosis (FSGS) — 15–20% - Membranoproliferative GN (MPGN) — 5–10% - IgA nephropathy (mixed nephrotic/nephritic) — 10–15%

### Nephritic Syndrome

**Definition:** Rapid GFR decline + hematuria (dysmorphic RBCs, RBC casts) + hypertension + mild-to-moderate proteinuria (<3.5 g/day, usually <1 g/day).

**Pathophysiology:** Proliferative inflammation (endocapillary or extracapillary) with immune complex deposition or direct cellular attack.

**Clinical Features:** - Hematuria dominant (red-tea colored urine from RBC casts) - Dysmorphic RBCs on microscopy (deformed by passage through damaged glomeruli) - RBC casts (virtually pathognomonic for glomerulonephritis) - Hypertension: significant (60–80% of patients) - Renal function: often acutely reduced (SCr ↑ over days/weeks) - Edema: mild (volume expansion from Na retention, not protein loss) - Proteinuria: <1–2 g/day (rarely nephrotic-range)

**BUN:Cr ratio:** May be elevated if severe (prerenal component from glomerulonephritis-induced volume expansion).

**Major Nephritic Diseases:** - Rapidly progressive GN (RPGN) — ANCA-associated, anti-GBM, immune complex - IgA nephropathy — most common GN worldwide - Post-infectious GN — especially post-streptococcal (PSGN) - Lupus nephritis — Class III (focal proliferative) or Class IV (diffuse proliferative) - MPGN — mixed presentation

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## Part 2: Serologic Workup Decision Tree

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GLOMERULONEPHRITIS SUSPECTED (proteinuria + hematuria ± renal dysfunction)
│
├─→ STEP 1: Determine Clinical Phenotype
│    ├─ NEPHROTIC (proteinuria >3.5 g/day, edema, hypoalbuminemia)
│    │    └─→ See Part 3 (Nephrotic Algorithm)
│    │
│    └─ NEPHRITIC (hematuria + RBC casts, rapid Cr rise, hypertension)
│         └─→ Continue to Step 2 below
│
├─→ STEP 2: Assess Complement Status
│    │
│    ├─ SERUM C3 + C4 MEASURED
│    │    │
│    │    ├─ NORMAL COMPLEMENT → Low-complement GN UNLIKELY
│    │    │    (Order: ANA, ANCA, SPEP/UPEP, complement-independent workup)
│    │    │
│    │    └─ LOW COMPLEMENT (C3 ↓ or C4 ↓) → Check C3-nephritic diseases
│    │         (Order: ANA, anti-dsDNA, anti-C1q, cryoglobulins)
│    │
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│   └─→ STEP 3: Order Targeted Serology Based on Clinical Context
│       │
│       ├─ Suspect ANCA-associated: ANCA (c-ANCA, p-ANCA), anti-PR3, anti-MPO
│       │
│       ├─ Suspect anti-GBM: anti-GBM antibodies (linear IgG IF pattern)
│       │
│       ├─ Suspect immune complex: ANA (for lupus), anti-dsDNA, anti-C1q
│       │
│     ├─ Suspect post-infectious: ASO titer, anti-hyaluronidase (coreopsis antigen)
│       │   (Often serologies negative; diagnosis clinical + kidney biopsy)
│       │
│     └─ Suspect glomerulonephritis of unclear type: SPEP/UPEP (monoclonal), cryoglobulins
│
└─→ STEP 4: Renal Biopsy (Proceed if workup suggestive or diagnosis unclear)
   └─→ Light microscopy (LM) + Immunofluorescence (IF) + Electron microscopy (EM)
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## Part 3: Comprehensive Serologic Panel

### Universal Initial Serologies (All Suspected GN)

| Test | Rationale | Normal Range |
|---|---|---|
| **Serum creatinine** | Baseline renal function | 0.7–1.3 mg/dL |
| **BUN** | Assess azotemia | 7–20 mg/dL |
| **Albumin** | Nephrotic range loss | >3.5 g/dL |
| **Complement: C3, C4, CH50** | Identify complement consumption | C3 >90 mg/dL; C4 >16 mg/dL |
| **Antinuclear antibody (ANA)** | Screen for lupus/SLE | <1:80 (negative) |
| **Cryoglobulins** | HCV-related; Type II MPGN | Negative |
| **Serum/urine protein electrophoresis** | Monoclonal protein; nephrotic range | No M-spike; urine PEI <150 mg/24h |
| **Renal ultrasound** | Assess kidney size, echogenicity | Normal-sized, normal echotexture |
| **Urinalysis with microscopy** | RBC casts, proteinuria quantification | <5 RBC/hpf; <1 RBC cast/lpf |

### Phenotype-Specific Serology (Nephritic Presentation)

**Low Complement (C3 ↓, C4 ↓)**

| Diagnosis | Serologic Markers | IF Pattern | EM Findings |
|---|---|---|---|
| **Lupus Nephritis (Class III–IV)** | ANA+, anti-dsDNA+, anti-C1q+, low C3/C4 | Granular IgG + C3 + IgA + IgM | Subendothelial deposits (hump) |
| **MPGN Type II (IC-MPGN)** | Low C3 ± C4, cryoglobulins±, anti-HCV± | Granular C3 + IgG (variable) | Intramembranous ("dense intramembranous") |
| **C3 Glomerulonephritis** | Very low C3, normal ANA/ANCA | C3 dominant (>IgG); ± C1q, ± FB | Electron-dense deposits in GBM/subendothelial |
| **Post-Streptococcal GN** | ASO titer+, anti-hyaluronidase+, low C3 (transient) | Granular C3 + IgG + IgM | Subhump, subepithelial "hump" deposits |

**Normal Complement (C3 Normal, C4 Normal)**

| Diagnosis | Serologic Markers | IF Pattern | EM Findings |
|---|---|---|---|
| **ANCA-Associated Vasculitis** | c-ANCA/anti-PR3+ OR p-ANCA/anti-MPO+, ANCA+ | Pauci-immune (minimal IF); ± ANCA+ | Fibrinoid necrosis; few deposits |
| **Anti-GBM Disease** | Anti-GBM+ (linear antibodies) | Linear IgG + C3 along GBM | GBM disruption; linear electron density |
| **IgA Nephropathy** | Normal; elevated IgA level (variable) | Dominant IgA (granular) | Electron-dense deposits in mesangium |
| **Atypical HUS / C3-dysregulation** | Complement gene mutations (CFH, CFI, C3); normal routine C3 unless active disease | C3 dominant IF | C3GN pattern or MPGN-like |

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## Part 4: Immunofluorescence (IF) Patterns and Diagnosis

### Linear IF Pattern (Anti-GBM)

**Finding:** Continuous linear IgG staining along glomerular basement membrane.

**Diagnosis:** Anti-GBM disease (Goodpasture syndrome if pulmonary hemorrhage).

**Associated Findings:** - Anti-GBM antibodies in serum (EIA) - RPGN on LM (crescents 50–95%) - Hemoptysis if pulmonary involvement - CXR: bilateral alveolar infiltrates

**Treatment:** Plasmapheresis + immunosuppression (pulse methylprednisolone + cyclophosphamide or rituximab).

### Granular IF Pattern (Immune Complex)

**Finding:** Granular or lumpy-bumpy deposits of IgG ± IgA ± IgM along GBM and mesangium.

**Associated Diagnoses:** - **High C3 + IgG:** Lupus nephritis (ANA+, anti-dsDNA+), PSGN (ASO+, recent strep) - **Dominant IgA:** IgA nephropathy (normal serologies except elevated serum IgA) - **IgA + C3:** IgA vasculitis (palpable purpura, abdominal pain, arthritis) - **IgM + C3:** IgM dominant MPGN, post-viral

**Treatment:** Varies by diagnosis; RAAS blockade universal.

### Pauci-Immune IF Pattern (ANCA-Associated Vasculitis)

**Finding:** Minimal or absent IF staining despite necrotizing crescents on LM (hence "pauci-immune").

**Serology:** ANCA+ (c-ANCA/PR3+ or p-ANCA/MPO+) in 90% of cases.

**Associated ANCA Status:** - **c-ANCA (PR3+):** Granulomatosis with polyangiitis (GPA); upper/lower respiratory involvement common - **p-ANCA (MPO+):** Microscopic polyangiitis (MPA), EGPA (eosinophilia); pauci-immune GN - **ANCA-negative (<10%):** Still pauci-immune GN; poor prognosis

**Treatment:** Induction (rituximab or cyclophosphamide) + maintenance immunosuppression.

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## Part 5: Electron Microscopy (EM) Localization

| EM Finding | Diagnosis | Clinical Pearl |
|---|---|---|
| **Subepithelial ("hump") deposits** | Post-streptococcal GN | Self-limited; resolves in weeks–months |
| **Subendothelial deposits** | Lupus, MPGN, PSGN | Associated with lower C3 (complement consumption) |
| **Intramembranous deposits** | MPGN Type II (DDD); C3GN variant | Tenacious; may progress; MPGN Type III has subepithelial tubular deposits |
| **Mesangial deposits** | IgA nephropathy, IgM nephropathy | IgA most common GN globally; hematuria-predominant presentation |
| **No deposits (pauci-immune)** | ANCA-associated RPGN, anti-GBM | IF confirms ANCA status or linear IgG |

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## Part 6: When to Biopsy (KDIGO 2021 Indications)

**Biopsy Indicated:** 1. **Presumed glomerulonephritis** with uncertain diagnosis 2. **Nephrotic syndrome** (except diabetic patient with classic nodular disease on imaging + DM hx >10 years + proteinuria >3.5 g/day) 3. **Hematuria + RBC casts** with negative serologies (to rule out ANCA-negative pauci-immune GN or atypical anti-GBM) 4. **SLE** with suspected lupus nephritis (determines class; guides treatment) 5. **Rapid progression** or poor response to

initial immunosuppression (rule out superimposed diagnosis) 6. **Atypical presentation** (e.g., nephrotic range proteinuria without classic hyperlipidemia; rapid GFR decline in 'stable' CKD)

**Biopsy Not Indicated:** - Diabetic with >10-year DM hx, nodular GS on imaging, nephrotic proteinuria, and normal serologies - Obvious PSGN (post-streptococcal with ASO titer+, depressed C3, typical presentation) if not severe/rapidly progressive - Known ANCA+ patient with new RPGN (strongly suggestive of continued ANCA-associated disease)

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## Part 7: Treatment Overview by Major GN Diagnosis

### Lupus Nephritis (All Classes)

**Induction (0–6 months):** - Corticosteroids (methylprednisolone 500 mg IV 3 days, then prednisone taper) - Cyclophosphamide (500 mg IV monthly ×6) OR mycophenolate mofetil (MMF 1–3 g/day) [both Class III agents]

**Maintenance (ongoing):** - Azathioprine 1–2 mg/kg/day OR MMF 2 g/day - Prednisone taper to lowest effective dose (<7.5 mg/day)

**Ancillary:** RAAS blockade (ACE-I/ARB), hydroxychloroquine 200–400 mg/day (plaque retinitis monitoring), NSAIDs if needed.

### ANCA-Associated Vasculitis (GPA, MPA)

**Induction (0–6 months):** - Methylprednisolone 500 mg IV 3 days, then prednisone taper - Rituximab 375 mg/m² IV weekly ×4 OR cyclophosphamide 15 mg/kg IV monthly ×3–6 months [Class I evidence for rituximab now]

**Maintenance:** - Rituximab 500 mg IV at 6 months, then every 6–9 months ×18–24 months - Azathioprine 1–2 mg/kg/day as alternative

**Special consideration:** ANCA-negative pauci-immune GN; treat as ANCA+ (poor outcomes if untreated).

### Anti-GBM Disease

**Emergency treatment (immediate plasmapheresis):** - Plasmapheresis 50 mL/kg/day for 7–14 days (remove circulating antibodies) - Parallel immunosuppression: methylprednisolone + cyclophosphamide (pulse then maintenance) - Continue until anti-GBM serology negative

**Prognosis:** Depends on presentation creatinine; >50% of untreated RPGN patients progress to ESRD within weeks.

### IgA Nephropathy

**Asymptomatic hematuria / mild proteinuria (<1 g/day):** - RAAS blockade alone (target BP <120/80) - Supportive care

**Proteinuria 1–3 g/day:** - RAAS blockade (maximum tolerated dose) - Add immunosuppression if proteinuria persists: methylprednisolone + MMF or corticosteroids alone (varies by guideline)

**Nephrotic proteinuria or RPGN:** - Aggressive immunosuppression (methylprednisolone + MMF/cyclophosphamide) - Plasmapheresis if RPGN presentation

### Membranous Nephropathy

**Asymptomatic proteinuria or <3.5 g/day:** - Observation + RAAS blockade - Remission rate 30% spontaneously

**Nephrotic syndrome (proteinuria >3.5 g/day + symptoms):** - Check phospholipase A2 receptor (PLA2R) serology (70% of idiopathic MN) - First-line: Corticosteroids + cyclophosphamide OR corticosteroids + MMF (alkylating agent alternating monthly with methylprednisolone pulses); rituximab emerging as alternative

**Secondary MN** (SLE, hepatitis B, NSAID): Treat underlying disease.

### Post-Infectious (Post-Streptococcal) GN

**Most cases self-limited; treat supportively:** - RAAS blockade (ACE-I) if proteinuria >0.5 g/day - Careful fluid/sodium management (volume overload common) - Corticosteroids NOT indicated unless severe (RPGN with >50% crescents)

**Follow-up:** Serial C3 levels (normalizes in 6–8 weeks if PSGN); creatinine should normalize in 3–6 months.

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## Related Resources

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

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## References


[1] Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int Suppl.* 2021;11:S1–S276. KDIGO Guidelines

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[4] Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013;65:1–11. PubMed

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