

# Nephritic vs. Nephrotic Syndromes: A Comprehensive Student Guide

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## Nephritic vs. Nephrotic Syndromes: A Comprehensive Student Guide

### Learning Objectives

By the end of this module, you will be able to:

1. **Define** nephrotic and nephritic syndromes and distinguish key clinical features
2. **Interpret** urine microscopy findings to differentiate between nephritic and nephrotic presentations
3. **Apply** complement testing to generate differential diagnoses
4. **Recognize** ANCA-associated vasculitis and anti-GBM disease presentations
5. **Develop** basic diagnostic and treatment approaches for each syndrome type

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### Core Definitions and Clinical Features

#### Nephrotic Syndrome

**Definition:** A clinical syndrome caused by increased glomerular permeability, characterized by massive proteinuria with secondary hypoalbuminemia, edema, and hyperlipidemia.

**Diagnostic Criteria:** - Proteinuria >3.5 g/day (or >40 mg/m<sup>2</sup>/hr in children) - Serum albumin <3.0 g/dL (hypoalbuminemia) - Edema (periorbital, peripheral, anasarca) - Hyperlipidemia (elevated cholesterol, triglycerides)

**Key Laboratory Finding:** Proteinuria often exceeds 10 g/day with predominantly albumin in the urine.

#### Nephritic Syndrome

**Definition:** A clinical syndrome characterized by inflammation of the glomeruli, resulting in hematuria, variable proteinuria, hypertension, and reduced kidney function.

**Diagnostic Criteria:** - Hematuria (often gross, with RBC casts) - Proteinuria (usually <3.5 g/day, non-nephrotic range) - Hypertension - Reduced glomerular filtration rate - Edema (less prominent than in nephrotic syndrome)

**Key Laboratory Finding:** Red blood cell casts in urine are pathognomonic for glomerulonephritis.

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## Comparative Table: Nephrotic vs. Nephritic Features

Feature	Nephrotic Syndrome	Nephritic Syndrome
<b>Proteinuria</b>	>3.5 g/day	<3.5 g/day
<b>Hematuria</b>	Minimal (<5 RBC/hpf)	Present (often gross)
<b>RBC Casts</b>	Absent	Present (diagnostic)
<b>Hypertension</b>	Variable	Common
<b>GFR</b>	Often preserved initially	Usually reduced
<b>Edema</b>	Marked (anasarca)	Mild to moderate
<b>Serum Albumin</b>	Low (<3 g/dL)	Normal or mildly low
<b>Cholesterol</b>	Markedly elevated	Normal or mildly elevated

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## Urine Microscopy: The Key Diagnostic Tool

### Nephrotic Syndrome Findings

**Oval Fat Bodies:** - Tubular epithelial cells containing lipid droplets - Appear as refractive cells with characteristic oval shape - Indicate tubular reabsorption of filtered lipoproteins

**Fatty Casts:** - Casts containing lipid droplets - Show “Maltese cross” appearance under polarized light microscopy - Pathognomonic for nephrotic syndrome - Result from tubular uptake and incorporation of lipid particles

**Waxy Casts:** - May indicate chronic kidney disease with severe proteinuria - Represent aged casts with degenerated cellular material

**Minimal Hematuria:** - Usually <5 RBCs/hpf - If hematuria is present and significant, consider overlap with nephritic disease

### Nephritic Syndrome Findings

**RBC Casts:** - Almost pathognomonic for glomerulonephritis - Presence indicates glomerular hematuria with tubular dysfunction - Single RBC cast mandates further glomerular disease workup

**Dysmorphic RBCs:** - Distorted morphology from passage through damaged glomeruli - Indicates glomerular origin of hematuria (vs. lower urinary tract bleeding) - Acanthocytes (particularly >5%) suggest active glomerulonephritis

**WBC Casts:** - May be present in proliferative glomerulonephritis - Suggest active inflammation within glomeruli

**Granular/Muddy Brown Casts:** - Represent cellular debris and hemoglobin casts - Indicate active glomerular inflammation - Common in acute glomerulonephritis

**Sterile Pyuria:** - Marked WBCs without bacteria - Seen in some proliferative glomerulonephritides - Rule out infection before attributing to glomerular disease

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## **Serological Evaluation: Complement Testing Strategy**

### **The Critical Role of Complement Measurements**

Always measure **C3 and C4 together** because: - Different patterns indicate different complement pathways activated - Classical pathway (C3 + C4 both low) suggests immune complex disease - Alternative pathway (C3 low, C4 normal) suggests infection or dysregulation - Both normal suggests vasculitis or other mechanisms

### **Low Complement Nephritic Syndromes**

**Low C3 + Low C4 (Classical Pathway Activation)** Strongly suggests immune complex disease: - **Systemic lupus erythematosus (SLE)** — must rule out with ANA, anti-dsDNA - **Cryoglobulinemia** — check cryoglobulin levels and hepatitis C - **Post-streptococcal glomerulonephritis** — recent pharyngitis or skin infection - **Subacute bacterial endocarditis** — blood cultures, echocardiography - **Shunt nephritis** — history of ventriculoperitoneal shunt

**Low C3, Normal C4 (Alternative Pathway Activation)** Suggests infection or complement dysregulation: - **Post-infectious glomerulonephritis** — ASO titers, streptococcal serology - **C3 glomerulopathy** — rare; requires electron microscopy and nephritic factors testing - **Dense deposit disease** — membranoproliferative pattern with electron microscopy

### **Normal Complement Nephritic Syndromes**

Normal serum complement indicates: - **IgA nephropathy** — most common primary GN worldwide - **ANCA-associated vasculitis** (GPA, MPA, EGPA) - **Anti-GBM disease** (Goodpasture syndrome) - **Thin basement membrane disease** - **Alport syndrome** — progressive renal disease with extrarenal features

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## **Key Nephritic Disease Entities: Recognition Patterns**

### **IgA Nephropathy**

**Clinical Presentation:** - Gross hematuria within 1-3 days of upper respiratory infection - “Tea-colored” or “cola-colored” urine common - Often in younger patients (20-40 years) - Most common primary GN globally

**Key Diagnostic Feature:** - Mesangial IgA deposits on kidney biopsy (immunofluorescence) - Dysmorphic RBCs and RBC casts in urine

**Complement Profile:** Normal C3 and C4

## ANCA-Associated Vasculitis

**Microscopic Polyangiitis (MPA) Antibody Pattern:** P-ANCA/MPO positive (70-80%) - Renal involvement in up to 80% of cases - Diffuse capillaritis on lung biopsy (when pulmonary involved) - Most commonly renal-limited disease

**Clinical Pearl:** MPA more likely to have renal involvement than GPA

**Granulomatosis with Polyangiitis (GPA, formerly Wegener's) Antibody Pattern:** C-ANCA/PR3 positive (90%) - Classic pulmonary-renal syndrome - **Upper respiratory involvement:** sinusitis, bloody nasal discharge, nasal ulceration - **Lower respiratory:** pulmonary infiltrates, hemoptysis - **Necrotizing granulomatous inflammation** distinguishes from MPA

**Diagnostic Confidence:** - C-ANCA positive + sinusitis + pulmonary infiltrates + RBC casts = 98% posttest probability of GPA

**Treatment Urgency:** Rapidly progressive glomerulonephritis; urgent biopsy and treatment

## Anti-GBM Disease (Goodpasture Syndrome)

**Definition:** Autoantibodies against NC1 domain of alpha-3 chain of type IV collagen

**Two Presentations:** 1. **Anti-GBM nephritis** — kidney involvement alone 2. **Goodpasture syndrome** — kidney + lung involvement with pulmonary hemorrhage

**Clinical Features:** - Rapidly progressive glomerulonephritis - Pulmonary hemorrhage (hemoptysis) in Goodpasture - Peak incidence: 20s (predominantly males) and 60s (equal sex distribution) - Crescent formation on biopsy

**Diagnostic Clue:** Linear IgG staining on immunofluorescence (vs. granular in immune complex disease)

**Complement Pattern:** Normal C3 and C4

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## Clinical Pearls for Syndrome Differentiation

**Pearl 1: RBC Casts = Glomerulonephritis** - Single RBC cast mandates evaluation for nephritic disease - Even minimal hematuria with RBC casts indicates glomerular origin

**Pearl 2: Complement Interpretation** - Serial complement determinations better than single measurements - Persistently depressed C3 >6-8 weeks suggests other diagnosis (lupus or MPGN) - Normal complement with nephritic presentation  suspect vasculitis or anti-GBM

**Pearl 3: Clinical Context Matters** - Recent infection  think post-infectious GN - Systemic symptoms (fever, arthritis, rash)  suspect vasculitis or SLE - Hemoptysis  consider anti-GBM or ANCA vasculitis

## Practice Questions

**Question 1:** A 24-year-old male presents with gross hematuria, mild hypertension, and reduced creatinine clearance 2 weeks after pharyngitis. Urinalysis shows 1.5 g/day proteinuria, dysmorphic RBCs, and RBC casts. Serum complement shows low C3, normal C4. What is the most likely diagnosis?

- A) Membranous nephropathy
- B) Post-streptococcal glomerulonephritis
- C) IgA nephropathy
- D) Minimal change disease

**Correct Answer: B** — Low C3 with normal C4 suggests alternative pathway activation typical of post-infectious GN. Recent pharyngitis supports this diagnosis. Post-infectious GN typically has minimal proteinuria and dysmorphic RBC casts.

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**Question 2:** A 35-year-old female presents with dyspnea, hemoptysis, hematuria, and RBC casts. Serologies show P-ANCA positive. What additional systemic feature would most help distinguish between microscopic polyangiitis and granulomatosis with polyangiitis?

- A) Cardiac involvement
- B) Sinusitis and upper respiratory involvement
- C) Peripheral neuropathy
- D) Glomerulonephritis severity

**Correct Answer: B** — GPA classically presents with upper respiratory involvement (sinusitis, nasal ulceration) and lower respiratory involvement along with renal disease. MPA typically presents with pulmonary capillaritis but no granulomatous inflammation or upper respiratory involvement.

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**Question 3:** A 55-year-old with nephrotic syndrome (8 g/day proteinuria, serum albumin 2.2 g/dL) is found to have lipiduria with oval fat bodies and fatty casts. Which finding would be LEAST expected in this patient?

- A) Edema
- B) RBC casts
- C) Hypercholesterolemia
- D) Low serum albumin

**Correct Answer: B** — Nephrotic syndrome classically shows minimal hematuria (<5 RBC/hpf) and does NOT show RBC casts. The presence of RBC casts would suggest overlap with nephritic disease or a mixed presentation requiring further evaluation.

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## Clinical Application: Integration Framework

When evaluating a patient with hematuria and proteinuria:

1. **Quantify proteinuria**

- 3.5 g/day  nephrotic range
  - <3.5 g/day  nephritic range
2. **Examine urine sediment**
    - RBC casts present  definitely nephritic
    - Fatty casts/oval fat bodies  nephrotic
  3. **Check complement levels**
    - Low C3 + Low C4  immune complex disease
    - Low C3 only  infection or dysregulation
    - Normal  vasculitis or anti-GBM disease
  4. **Obtain serology based on pattern**
    - Low complement  ANA, anti-dsDNA, cryoglobulins
    - Normal complement  ANCA, anti-GBM, ASO titers
  5. **Proceed to kidney biopsy** for definitive diagnosis when diagnosis remains unclear
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## See Also

### Related Student Handouts

- Lupus Nephritis
- IgA Nephropathy
- Vasculitis and Complement-Mediated Diseases
- FSGS: Focal Segmental Glomerulosclerosis
- Glomerular Treatment Principles
- Kidney Biopsy Essentials

### Clinical Content (01-Clinical-Medicine/Nephrology)

- Glomerular Diseases Hub
- Essential Renal Laboratory Tests

### Butler-COM Resources

- Butler COM - Nephrology Deep Dive
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### Related Topics to Explore

- Treatment of Glomerular Diseases
  - Lupus Nephritis
  - IgA Nephropathy
  - ANCA-Associated Vasculitis
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## Summary

Understanding the distinction between nephrotic and nephritic syndromes is fundamental to nephrology practice. Nephrotic syndrome emphasizes **massive proteinuria** with **preserved**

**GFR** initially, while nephritic syndrome presents with **hematuria** and **RBC casts** indicating **active glomerular inflammation** with **declining GFR**. Complement testing and serological evaluation guide diagnosis toward specific entities. Recognition of these patterns enables rapid diagnosis, appropriate referral for biopsy, and timely immunosuppressive therapy to prevent irreversible kidney damage.

### **Clinical Resources**

- Clinical Review: Nephrotic Nephritic Review — Comprehensive clinical review with PubMed references