

# Lupus Nephritis: Classification, Prognostication, and Treatment

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## Lupus Nephritis: Classification, Prognostication, and Treatment

### Learning Objectives

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

1. **Classify** lupus nephritis using ISN/RPS criteria and prognosticate using activity/chronicity indices
2. **Recognize** serologically quiet lupus nephritis and understand its implications
3. **Distinguish** between histologic activity and clinical activity
4. **Apply** risk stratification to select appropriate immunosuppressive regimens
5. **Integrate** serologic monitoring with biopsy findings for treatment decision-making

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### Executive Summary: Lupus Nephritis in Context

**Epidemiology:** - Affects 25-60% of patients with systemic lupus erythematosus - Leading cause of morbidity, mortality, and ESRD progression in young adults - Disproportionately affects women of African American, Hispanic, and Asian descent

**Prognosis Without Treatment:** - 5-year survival with untreated proliferative nephritis: ~17%  
- Modern treatment: 70-90% of patients achieve remission

**Key Teaching Point:** Lupus nephritis is a **medical emergency requiring prompt diagnosis and aggressive immunosuppression** to prevent irreversible kidney damage.

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### ISN/RPS Classification System

The standard histologic classification for lupus nephritis uses six classes based on light microscopy findings:

Class	Description	Typical Presentation	GFR Impact
<b>I</b>	Minimal mesangial	Minimal proteinuria, microscopic hematuria	Preserved
<b>II</b>	Mesangial proliferative	Mild-moderate proteinuria, hematuria	Preserved initially
<b>III</b>	Focal proliferative (<50% glomeruli)	Proteinuria, hematuria, variable GFR decline	Variable
<b>IV</b>	Diffuse proliferative (≥50% glomeruli)	Nephrotic/nephritic features, often GFR decline	Impaired
<b>V</b>	Membranous	Nephrotic syndrome, usually preserved GFR	Preserved initially
<b>VI</b>	Advanced sclerotic (>90% sclerosed)	ESRD, minimal active disease	Severely reduced

**Clinical Pearl:** Classes III and IV represent proliferative lupus nephritis requiring aggressive immunosuppression. Class IV (diffuse) carries worse prognosis than Class III (focal).

### Activity and Chronicity Indices: Prognostication Framework

Beyond simple classification, semiquantitative scoring systems provide powerful prognostic information:

#### Modified NIH Activity Index (Maximum 24 points)

Lesion	Extent Scoring	Weighting
Endocapillary hypercellularity	0-3 (% of glomeruli)	×1
Neutrophils/karyorrhexis in loops	0-3	×1
<b>Fibrinoid necrosis</b>	0-3	<b>×2</b>
<b>Cellular/fibrocellular crescents</b>	0-3	<b>×2</b>
Hyaline deposits (wire loops)	0-3	×1
Interstitial inflammation	0-3	×1

**Note:** Fibrinoid necrosis and crescents are weighted ×2 due to worse prognostic implications.

**Interpretation:** - **Low activity:** AI 0-5 - **Moderate activity:** AI 6-11 - **High activity:** AI 12-24

#### Modified NIH Chronicity Index (Maximum 12 points)

Lesion	Extent Scoring
Global/segmental glomerulosclerosis	0-3
Fibrous crescents	0-3

Lesion	Extent Scoring
Tubular atrophy	0-3
Interstitial fibrosis	0-3

**Interpretation:** - **Low chronicity:** CI 0-2 - **Moderate chronicity:** CI 3-5 - **High chronicity:** CI 6-12

## Critical Prognostic Principle

### Chronicity Index is More Predictive Than Activity Index

This counterintuitive finding reflects that: - **Activity Index** = current treatable inflammation (high activity = many options for response) - **Chronicity Index** = irreversible damage already done (cannot be reversed by treatment)

**Real-World Implication:** A patient with Activity Index 18 (high) but Chronicity Index 2 (low) has BETTER long-term outcomes than one with Activity Index 8 (moderate) and Chronicity Index 8 (high). The baseline damage (chronicity) predicts outcome more than current inflammation (activity).

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## Serologically Quiet Lupus Nephritis: An Under-Recognized Phenomenon

### Definition and Prevalence

Serologically quiet lupus nephritis describes patients with: - **Active histological disease** on kidney biopsy - **Normal or near-normal serologies** (low anti-dsDNA, normal complement levels) - Occurs in 15-40% of lupus nephritis cases

**Critical Clinical Pearl:** Normal serologies do NOT exclude active lupus nephritis. Biopsy findings, not serology, guide treatment decisions.

### Mechanistic Explanations for Serological Discordance

**In Situ Immune Complex Formation** Rather than circulating complexes depositing in kidneys, autoantibodies bind directly to antigens **within the kidney**, consuming complement locally without systemic depletion. Inflammation occurs entirely in the renal microenvironment.

**Tissue-Resident B Cells and Tertiary Lymphoid Structures** Emerging evidence shows that B cells establish residence within inflamed kidneys, forming organized tertiary lymphoid structures (TLS): - Local antibody production without significant serum elevation - Clonal expansion and somatic hypermutation occurring locally - Different immunophenotype than circulating B cells - May be more resistant to anti-CD20 antibodies

**Treatment Implication:** Obinutuzumab (potent B-cell depletion) may be more effective than rituximab in serologically quiet disease due to better tissue penetration.

**Alternative Autoantibody Specificities** Autoantibodies other than anti-dsDNA may drive disease: - Anti-C1q antibodies - Anti-nucleosome antibodies - Anti-Ro/La, anti-Smith antibodies - Antibodies to intracellular antigens ( $\alpha$ -enolase, annexin A2)

**Clinical Application:** Anti-C1q antibodies may be positive in serologically quiet lupus nephritis and could serve as an alternative activity marker.

## Monitoring Implications for Serologically Quiet Disease

Since traditional serology cannot track disease activity:

1. **Quantify serial proteinuria** (most sensitive marker of glomerular activity)
2. **Track serum creatinine and eGFR** trends
3. **Examine urine sediment** for active casts and dysmorphic RBCs
4. **Consider anti-C1q antibodies** if initially positive
5. **Plan repeat kidney biopsy** at 6-12 months if clinical response unclear

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## Renal-First Lupus: A Special Presentation

### Epidemiology

Approximately 10-20% of lupus nephritis presents as: - Biopsy-proven lupus nephritis - **No prior SLE diagnosis** - **Minimal or absent extrarenal manifestations** - Sometimes completely seronegative

### Diagnostic Characteristics

**Classic Renal-First:** - Positive ANA, elevated anti-dsDNA, hypocomplementemia - Straightforward SLE diagnosis despite absent systemic symptoms

**Serologically Attenuated:** - Positive ANA but negative anti-dsDNA, normal complements

**Completely Seronegative:** - Negative anti-dsDNA, normal complements, negative ANA - Diagnosis rests entirely on kidney biopsy findings

### Histologic Confirmation in Seronegative Cases

**“Full House” Immunofluorescence Pattern:** - Staining for IgG, IgA, IgM, C3, **and C1q** - C1q deposition is highly specific for lupus nephritis - Rarely seen in other glomerular diseases

**Electron Microscopy:** - Electron-dense deposits in mesangial, subendothelial, and subepithelial locations - Tubuloreticular inclusions (“interferon footprints”) in endothelial cells

**Light Microscopy:** - Endocapillary proliferation - Wire-loop deposits - Hyaline thrombi - Necrotizing lesions

### Pathophysiologic Hypothesis

Seronegative renal-first lupus may represent: - Primary renal immune dysregulation from local triggers (infection, ischemia) - Establishment of renal tertiary lymphoid structures - Local autoan-

tibody production consumed in situ - Absence of systemic autoimmunity explaining minimal extrarenal manifestations

## Natural History

- **Conversion to systemic SLE:** 30-50% develop extrarenal manifestations within 5-10 years
- **Renal outcomes:** Some evidence suggests slightly better outcomes than SLE with systemic involvement
- **Treatment:** Histology dictates intensity regardless of serologies or prior SLE diagnosis

**Key Teaching Point:** A patient with biopsy-proven Class IV lupus nephritis, activity index 9/24, chronicity index 8/12 requires aggressive triple immunosuppression regardless of whether they have positive serology, prior SLE diagnosis, or extrarenal symptoms.

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## Clinical Activity Assessment: SLEDAI and SLE-DAS

### SLEDAI-2K Scoring System

The Systemic Lupus Erythematosus Disease Activity Index is the most widely used clinical activity tool.

### Renal Domain (SLEDAI-R) Components:

Each item scores 4 points: - **Hematuria:** >5 RBCs/hpf (excluding stone, infection, other causes) - **Pyuria:** >5 WBCs/hpf (excluding infection) - **Urinary casts:** Heme-granular or RBC casts - **Proteinuria:** >0.5 g/24h or UPCr >0.5

**Overall SLEDAI Score Interpretation:** - SLEDAI  $\geq$ 3-4: Active disease - SLEDAI  $\geq$ 6: High activity - SLEDAI  $\geq$ 12: Severe flare

**Limitations:** - Includes serological markers (anti-dsDNA, complement) that may not reflect tissue disease activity in seronegative patients - Does not differentiate between Class II and Class IV nephritis severity

### SLE-DAS (SLE Disease Activity Score)

- Introduced 2019 as continuous measure
- Moderate correlation with SLEDAI ( $r=0.70$ )
- May better capture partial improvements
- Categories: remission, mild, low, moderate/severe

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## Treatment Framework: Histology-Guided Intensity

### Class I-II Lupus Nephritis

**Treatment:** Conservative management - Hydroxychloroquine (all patients) - Blood pressure control - RAAS blockade if any proteinuria - Monitor for progression

## **Class III-IV Proliferative Lupus Nephritis**

### **Induction Regimen (3-6 months):**

Option A: **MMF-based (preferred in many centers)** - Mycophenolate mofetil 1-3 g/day - Corticosteroids (tapered to lowest effective dose) - Hydroxychloroquine

Option B: **Cyclophosphamide (for crescentic or rapidly progressive disease)** - IV cyclophosphamide 500-1,000 mg/m<sup>2</sup> × 6 pulses - Corticosteroids - Hydroxychloroquine

**Maintenance (≥2-3 years):** - Mycophenolate mofetil or azathioprine - Low-dose corticosteroids (goal ≤7.5 mg/day prednisone) - Hydroxychloroquine (all patients)

**All Patients:** - Hydroxychloroquine 200-400 mg daily (reduces flares, mortality benefit, prevents systemic disease)

## **Class V Membranous Lupus Nephritis**

**First-line:** - Calcineurin inhibitors (cyclosporine or tacrolimus) - Low-dose corticosteroids - Mycophenolate mofetil (alternative)

### **Crescentic Lupus Nephritis (>50% Crescents)**

Indicates aggressive disease: - Consider induction cyclophosphamide (rather than MMF monotherapy) - More intensive corticosteroids initially - Earlier consideration of biologic therapy

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## **New and Emerging Therapies: The Biologic Era**

### **Belimumab (Anti-BLyS)**

- First biologic approved specifically for lupus nephritis (2020)
- B-cell activating factor inhibitor
- Added to standard induction regimens
- BLISS-LN trial showed improved hematologic response

### **Voclosporin (Calcineurin Inhibitor)**

- FDA-approved for lupus nephritis (2021)
- More selective and less nephrotoxic than traditional CNIs
- Combined with mycophenolate mofetil

### **Obinutuzumab (Anti-CD20)**

- Potent B-cell depletion antibody
- FDA approval pending (October 2025)
- Type II anti-CD20 with enhanced tissue penetration
- May be particularly effective in serologically quiet disease
- REGENCY trial showed benefit in high-proteinuria patients

## Practice Questions

**Question 1:** A 28-year-old female with SLE presents with nephrotic syndrome. Kidney biopsy shows Class IV proliferative lupus nephritis with activity index 16/24 and chronicity index 3/12. She is seronegative (normal anti-dsDNA, normal complement, negative anti-C1q). What is the most appropriate next step?

- A) Reassure that seronegative disease is mild and defer immunosuppression
- B) Initiate MMF-based induction therapy regardless of seronegative status
- C) Wait for serologies to become positive before treating
- D) Consider renal transplantation given seronegative status

**Correct Answer: B** — Histology dictates treatment intensity, not serology. Class IV with high activity index requires aggressive immunosuppression regardless of seronegative status. Seronegative disease reflects tissue-resident pathology, not milder disease.

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**Question 2:** At 6-month follow-up on mycophenolate therapy, a lupus nephritis patient has normalized anti-dsDNA titers and normal complement levels, yet continues 2 g/day proteinuria with stable creatinine. What is the most reasonable interpretation?

- A) Complete clinical remission has been achieved
- B) Therapy is failing and cyclophosphamide should be added
- C) Serologic remission achieved but clinical remission incomplete; continue current regimen
- D) Patient is developing steroid resistance

**Correct Answer: C** — Serologic remission (normalized serology) does not equal clinical remission (normalized proteinuria and creatinine). Persistent significant proteinuria despite serologic improvement requires continued or intensified therapy. This patient needs reassessment and possibly therapy adjustment.

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**Question 3:** Which of the following features is MOST associated with poor long-term kidney outcomes in lupus nephritis?

- A) Activity index 12/24
- B) Chronicity index 8/12
- C) Positive anti-dsDNA antibodies
- D) Elevated NT-proBNP at baseline

**Correct Answer: B** — Chronicity index (representing irreversible structural damage) is the most powerful predictor of long-term kidney outcomes. Activity index reflects treatable inflammation, so high activity is actually compatible with good outcomes if remission is achieved. Chronicity reflects permanent damage that cannot be reversed.

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## Clinical Pearl Summary

1. **Biopsy findings dictate treatment**, not serology alone
2. **Chronicity > Activity** for prognostication
3. **Serologically quiet disease is NOT mild disease** — it reflects tissue-resident pathology

4. **Hydroxychloroquine is essential** for all lupus nephritis patients
  5. **Early diagnosis and rapid immunosuppression** prevent irreversible damage
  6. **Repeat biopsy** appropriate when clinical response unclear
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## See Also

### Related Student Handouts

- Nephritic and Nephrotic Syndromes
- Vasculitis and Complement-Mediated Diseases
- Glomerular Treatment Principles
- Kidney Biopsy Essentials
- Immunosuppressive Therapy in Nephrology

### 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

- Serologically Quiet Lupus
  - Systemic SLE Management
  - Nephritic-Nephrotic Syndromes
  - Immunosuppressive Treatment in Glomerular Disease
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## Summary

Lupus nephritis remains a leading cause of kidney failure in young women despite treatment advances. Understanding the distinction between histologic activity (treatable) and chronicity (permanent damage) enables appropriate prognostication. Recognition that 15-40% of cases are serologically quiet prevents dangerous delays in diagnosis and treatment. Modern biologic therapies including belimumab and obinutuzumab expand treatment options and improve outcomes. Early diagnosis, prompt kidney biopsy, and aggressive immunosuppression guided by histology and clinical response remain the cornerstones of optimizing outcomes in this potentially devastating manifestation of SLE.