REVIEW ARTICLE

# Lupus Nephritis: A Literature Review

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**ABSTRACT**

Systemic lupus erythematosus (SLE) manifests with diverse clinical presentations, notably including lupus nephritis (LN), characterized by elevated morbidity and mortality rates, the latter being twice that of non-nephritis cases. A comprehensive understanding of the epidemiology, classification, diagnosis, and management of LN is essential for medical practitioners. The preponderance of female individuals, particularly during puberty and childbearing age, emphasizes the necessity for specialized attention in clinical contexts. The diagnostic process involves an initial clinical examination to capture the disease's clinical profile, followed by supportive laboratory assessments aimed at identifying indications of kidney damage or general SLE symptoms, often featuring proteinuria. Integral to the diagnostic journey is the gold standard kidney biopsy examination for LN, supplemented by the antinuclear antibodies (ANA) test serving as a primary criterion in diagnostic evaluations. Therapeutic strategies are intricately tailored based on clinical and biopsy findings, categorized into five distinct classes (normal, mesangial, focal and segmental proliferative, diffuse proliferative, and membranous) according to World Health Organization (WHO) classification. The precise implementation of therapeutic interventions holds the potential to significantly enhance the overall prognosis of LN, underscoring the pivotal role of accurate diagnosis and targeted management in optimizing patient outcomes.

**Keywords:** SLE; lupus nephritis; kidney manifestation; non-communicable disease

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## INTRODUCTION

Lupus nephritis (LN) is a major risk factor for morbidity and mortality in systemic lupus erythematosus (SLE). SLE is an autoimmune disease that has a variety of clinical symptoms because it attacks multi systemically (Justiz Vaillant et al., 2021), and can even cause chronic inflammation (Yen & Singh, 2018). As many as 35% of SLE sufferers in the United States show clinical symptoms that suggest nephritis (Zubair & Frieri, 2013). This is a situation where there is inflammation of the kidneys which can inhibit their function in filtering blood, causing several signs of abnormalities such as proteinuria, hematuria (Justiz Vaillant et al., 2021). The standardized mortality rate in LN patients is twice as high as in non-nephritis SLE patients (Moe et al., 2019).

LN usually occurs in the early course of SLE. Proteinuria is an early sign of LN, where there is tubular or glomerular dysfunction found in the presence of foamy urine or frequent urge to urinate at night (nocturia). A study found that 100% of patients suffering from LN experience proteinuria (Almaani et al., 2017). Suspicion of LN increases if the patient also suffers from hypertension, hematuria, proteinuria, lower extremity edema, and increased creatinine (Justiz Vaillant et al., 2021). Symptoms that are directly related to hypertension usually include dizziness, headaches, visual disturbances, and signs of heart problems (Musa et al., 2023).

## OBJECTIVE

The primary objective of this study is to comprehensively elucidate the clinical manifestations and diagnostic assessments associated with lupus, thereby contributing to a more profound understanding of the disease spectrum. Additionally, our aim is to tailor therapeutic interventions based on the severity of each individual's presentation, with the overarching goal of optimizing patient outcomes and ameliorating the overall prognosis of lupus. Through a meticulous examination of clinical features and the implementation of appropriate therapeutic strategies, we seek to advance the current understanding of lupus pathology and enhance the efficacy of targeted interventions, ultimately fostering improved patient care and management within the realm of autoimmune diseases.

## DISCUSSION

SLE predominantly affects women of childbearing age, but when it occurs in men, the prognosis is often more severe (Kuhn et al., 2015). Men diagnosed with SLE are more likely to have kidney involvement and are diagnosed at an older age compared to women (Tan et al., 2012). A study in Sweden from 2008 to 2021 identified 126 new SLE cases, with 28.6% of patients diagnosed with LN. Among them, 25% were male, and 75% were female (Arkema et al., 2023). Onset of SLE typically occurs during puberty. In children, SLE tends to be more severe than in adults, with a higher incidence of malar rash, nephritis, pericarditis,

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Table 1. Original World Health Organization (WHO) classification of lupus nephritis (IRA, 2019)

| Class | Pattern | Place of deposit of immune complexes | Sediment | Proteinuria (24 hour) | Creatinine Serum | Blood pressure | Anti-dsDNA | C3/C4 |
|---|---|---|---|---|---|---|---|---|
| I | Normal | There isn't any | There isn't any | <200mg | Normal | Normal | Negative | Normal |
| II | Mesangial | Mesangial | Erythrocytes/absent | 200-500mg | Normal | Normal | Negative | Normal |
| III | Focal and segmental proliferative | Mesangial subendotelial, ± subepithelial | Erythrocytes, leukocytes | 500-3500mg | Normal to mildly increased | Normal to slightly increased | Positive | Decrease |
| IV | Diffuse proliferative | Mesangial subendotelial, ± subepithelial | Erythrocytes, leukocytes, cylinders, erythrocytes | 1000-3500mg | Normal to depending on dialysis | Height | Positive to high titer | Decrease |
| V | Membranous | Mesangial subepithelial | There isn't any | >3000mg | Normal to slightly increased | Normal | Negative to moderate titer | Normal |

hematologic abnormalities, and hepatosplenomegaly. In elderly individuals, SLE can be more dangerous, involving organs such as the lungs and causing other complications like Raynaud's disease, malar rash, nephritis, and neuropsychiatric issues (Tsai et al., 2022). According to Hocaoglu et al (2022), there were 72 patients with incident NL between 1976–2018. The mean age at diagnosis was 38.4 years (SD 16.24), 76% of patients were female. The average annual incidence of NL between 1976 and 2018 was highest in the 30-39 year age group.

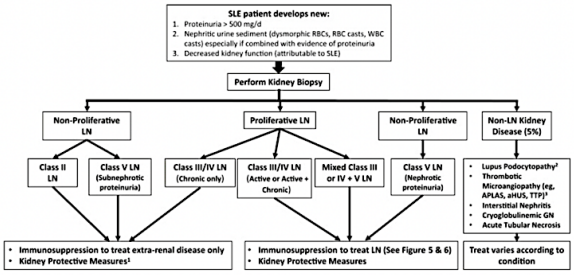


Figure 1. Diagnosis of Lupus Nephritis (Parikh et al., 2020)

This autoimmune disease represents an abnormal interaction between innate and adaptive immunity, triggering the formation of autoantibodies, and immunological disturbances that will impact various organ systems, including the kidneys (Yap & Chan, 2019). The formation of autoantibodies and autoreactivity is mediated by B cells of the adaptive immune system, T cells, and IFN-producing dendritic cells (Perl et al., 2022). B cells and T cells play crucial immunological roles related to the pathogenesis of SLE and LN, such as autoantigen presentation and proinflammatory cytokine secretion, resulting in the production of autoantibodies and sustaining the disease through the accumulation of autoreactive memory T cells (Suarez et al., 2016). Class I and II NL usually result in normal or normal kidney function low-grade proteinuria, sometimes accompanied by microscopic hematuria. Class III, IV, and V LNs were found on renal biopsy with extensive intrarenal inflammation.

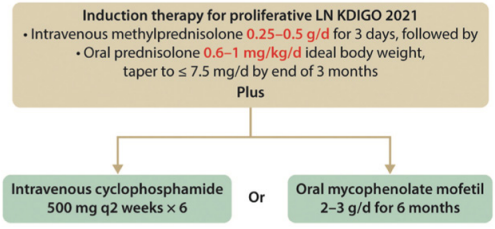


Figure 2. Induction therapy for proliferative LN (Rovin et al, 2021)

For SLE patients with compromised kidney function, routine laboratory tests, including blood urea nitrogen (BUN), serum creatinine, urinalysis for protein/casts, and 24-hour urine tests for creatinine and protein excretion, are essential to detect possible lupus nephritis (LN). Active LN is indicated by a 30% decrease in creatinine clearance, proteinuria (defined as ≥ 0.5 g/24 h), and findings from renal biopsies confirming active LN. Additionally, screening tests for worsening SLE include anti-dsDNA, complement C3 C4, ESR, or C-reactive protein In cases with a clinical history or lab results suggesting active nephritis, or in patients with recurrent nephritis episodes, a biopsy read by a pathologist is crucial for assessing disease progression, classification, prognosis, and distinguishing between active and chronic processes, as treatment approaches vary (Zubair, 2023; KDIGO, 2023). The ANA test is a primary criterion in diagnostic examinations, its role dependent on antibody specificity, quantity, and triggering antigens, mediating inflammation (Pisetsky & Lipsky, 2020).

The initial approach to treating LN involves the administration of intravenous methylprednisolone in conjunction with lower doses of oral prednisone, utilizing a tapering-off method. First-line immunosuppressive therapy encompasses a combination of mycophenolate mofetil (MMF) and low doses of cyclophosphamide (CYC). Antimalarial drugs play a pivotal role in reducing relapse rates. The therapeutic objective is to attain normal proteinuria levels within a 12-month timeframe, adhering to the 2019 EULAR/ERA-EDTA recommendations. Disease progression is systematically assessed every third, sixth, and twelfth month, with a specific focus on achieving a ≥25% reduction in proteinuria and maintaining a stable glomerular filtration rate (GFR) (Fanouriakis et al, 2020; KDIGO 2023).

For individuals with class I and II LN, the treatment protocol involves initiating glucocorticoid monotherapy, with approximately 90% of patients experiencing recovery within a median period of 4 weeks. The subsequent maintenance phase integrates low-dose glucocorticoids with additional agents, such as mycophenolic acid analogues (MPAA), azathioprine, or calcineurin inhibitors (CNI), particularly for patients with a history of relapse.For active proliferative LN, the initial or induction treatment involves administering low-dose intravenous cyclophosphamide (CYC) or mycophenolate mofetil (MMF) in combination with glucocorticoids, intravenous methylprednisolone, and subsequently, oral prednisone. In addressing class III or IV LN, the selection of initial treatment options necessitates a careful evaluation of both short-term and long-term responses, taking into account potential side effects such as infection and toxicity. Class V LN is treated with medications from the renin-angiotensin system blockade, hypertension drugs, immunosuppressives, and hydroxychloroquine (KDIGO, 2023).

Glucocorticoids thus also play a crucial role in all LN treatment plans, given their immunosuppressive and anti-inflammatory effects, making them effective in managing inflammation in patients with both class III and IV LN. Corticosteroids and immunosuppressants have consistently emerged as the predominant therapies prescribed for LN patients in several studies (Tjan et al., 2022; Diagne et al., 2020; Hailu et al., 2022). The 10-year survival rate experiences a notable enhancement, rising significantly from 46% to an impressive 95%, contingent upon the attainment of disease remission, as indicated by Almaani et al. in their 2017 study. This underscores the pivotal impact of achieving remission on the long-term prognosis, emphasizing the potential for substantial improvements in patient outcomes over the specified timeframe (Almaani et al, 2017).

## CONCLUSION

Lupus nephritis typically manifests with symptoms such as hypertension, hematuria, proteinuria, lower extremity edema, and elevated creatinine levels. Predominantly affecting women, particularly during puberty or childbearing age, LN can present more severe symptoms in children and poses heightened risks in older individuals, involving additional organs like the lungs. Proteinuria serves as an early indicator of LN, which stems from renal lesions or inflammation triggered by immune complexes, inducing inflammatory and cytotoxic reactions. The disease's severity is classified into five classes according to the World Health Organization (WHO). Laboratory tests and kidney biopsy constitute crucial diagnostic approaches, enabling accurate identification. Treatment strategies are tailored according to the specific LN class, underlining the importance of a nuanced and targeted therapeutic approach for optimal patient care

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## CONFLICT OF INTEREST

None to declare

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None to declare

## AUTHOR CONTRIBUTION

All author have contributed to all procss in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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