INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Recent Advances in the Diagnosis and Management of Lupus Nephritis in Systemic Lupus Erythematosus

Saja N*, Sajitha G

Department of Pharmacy Practice, College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram, Kerala, India

ARTICLE INFO

Published: 31 July 2026
Keywords:
lupus nephritis, systemic lupus erythematosus, biomarkers, belimumab, voclosporin, precision medicine.
DOI:
10.5281/zenodo.21727270

ABSTRACT

Lupus nephritis (LN) is one of the most severe organ manifestations of systemic lupus erythematosus (SLE), affecting 40–60% of patients over the course of the disease and representing a leading cause of chronic and end-stage kidney disease. Despite significant advances in understanding its immunopathogenesis, LN remains associated with substantial morbidity, mortality, and healthcare burdens worldwide. Early diagnosis and prompt initiation of appropriate therapy are essential to prevent irreversible renal damage and improve long-term outcomes. Conventional diagnostic approaches, including urinary protein quantification, serum complement levels, anti-double-stranded DNA antibody testing, and kidney biopsy, continue to be cornerstones of diagnosis. However, recent advances in molecular biomarkers, multi-omics technologies, artificial intelligence (AI)-assisted pathology, and precision medicine have transformed the diagnostic landscape. Therapeutically, the introduction of targeted biological agents, such as belimumab, cyclosporin, and emerging B-cell-directed therapies, has significantly improved renal response rates while reducing disease flares. Updated recommendations from the Kidney Disease: Improving Global Outcomes (KDIGO), the American College of Rheumatology (ACR), and the European Alliance of Associations for Rheumatology (EULAR) advocate individualized treatment strategies that integrate conventional immunosuppressive agents with novel biologics. This narrative review summarizes recent advances in the pathogenesis, diagnosis, biomarker development, and management of lupus nephritis, with particular emphasis on current evidence, evolving therapeutic strategies, and future perspectives in precision medicine.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by autoantibodies against nuclear antigens, immune complex deposition, and chronic inflammation in classic target organs, including the skin, joints, and

***Corresponding Author:** Saja N
Address: *College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram, Kerala, India*
Email ✉: sajasafeern@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

kidneys (1). The disease primarily affects women of reproductive age and exhibits a wide range of clinical manifestations, from minor mucocutaneous involvement to potentially fatal renal and neurological complications (2). One of the most severe forms of SLE is lupus nephritis (LN), which continues to be a significant global factor in morbidity, mortality, and medical costs. During the course of their illness, 40–60% of SLE patients experience clinically significant renal involvement, with the highest incidence in the first 5 years after diagnosis (3).

A high index of suspicion should be maintained for patients of Asian, African/Caribbean, and Hispanic descent because the incidence of LN varies by age and race/ethnicity(3). Socioeconomic disparities, delayed diagnosis, limited access to specialized care, and genetic susceptibility further contribute to adverse outcomes. Despite improvements in immunosuppressive therapy over recent decades, nearly 10–30% of patients with proliferative LN ultimately progress to end-stage kidney disease (ESKD), requiring dialysis or kidney transplantation(4).

The pathogenesis of lupus nephritis (LN) is a multifactorial process involving a complex interplay of genetic susceptibility, epigenetic modifications, environmental exposures, hormonal influences, and immune dysregulation(5). Defective clearance of apoptotic cells results in persistent exposure to nuclear autoantigens, which stimulates the production of pathogenic autoantibodies, particularly anti-double-stranded DNA (anti-dsDNA) antibodies(6). These autoantibodies form circulating immune complexes that deposit within the glomeruli, leading to complement activation, inflammatory cell recruitment, and the release of pro-inflammatory cytokines and chemokines that contribute to progressive renal injury(7). Recent studies have identified important pathogenic mechanisms involving B lymphocytes, T-helper cells, plasmacytoid dendritic cells, type I interferon signaling, neutrophil extracellular traps (NETs), and complement pathways, providing the basis for targeted and precision-based therapeutic strategies in LN (8).

Early identification of lupus nephritis (LN) remains a major clinical challenge, as conventional laboratory investigations may not detect ongoing renal inflammation before permanent kidney injury develops. Standard diagnostic assessment includes urinalysis, quantification of proteinuria, evaluation of serum creatinine and estimated glomerular filtration rate (eGFR), measurement of complement levels, anti-double-stranded DNA (anti-dsDNA) antibody titers, and renal biopsy. Although kidney biopsy remains the gold standard for confirming the diagnosis and determining histopathological class, its invasive nature limits its use for serial monitoring during long-term follow-up(3). Consequently, increasing attention has been directed toward the development of non-invasive biomarkers that can accurately assess disease activity, predict therapeutic response, and identify patients at risk of renal relapse(9). Urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), vascular cell adhesion molecule-1 (VCAM-1), and kidney injury molecule-1 (KIM-1) have demonstrated considerable potential for improving the diagnosis and prognostic assessment of LN(10). Recent advances in proteomics, transcriptomics, and other high-throughput molecular technologies have further accelerated biomarker discovery and are paving the way for precision diagnostic approaches in LN.

(11) Comprehensive evaluation of emerging biomarkers continues to strengthen their potential role in individualized disease monitoring and therapeutic decision-making (7).

The therapeutic management of LN has evolved considerably over the past decade, with the introduction of targeted biological agents alongside conventional immunosuppressive therapy (12). Historically, induction treatment relied primarily on high-dose glucocorticoids in combination with cyclophosphamide or mycophenolate mofetil (MMF), strategies that significantly improved renal outcomes but were frequently associated with treatment-related toxicity and disease relapse (3). The BLISS-LN trial demonstrated that the addition of belimumab to standard therapy significantly improved renal response and reduced the likelihood of disease progression in patients with active LN(13). Likewise, the AURORA trial showed that ciclosporin combined with standard-of-care therapy produced higher complete renal response rates than standard therapy alone14 (14). More recently, therapies targeting CD20-positive B cells, including obinutuzumab, together with other biologic agents directed against key immune pathways, have expanded the therapeutic options available for patients with LN (15).

Current clinical practice guidelines recommend an individualized treatment approach based on renal histology, disease severity, patient characteristics, and treatment response to optimize long-term renal outcomes. These recommendations advocate minimizing glucocorticoid exposure, using combination immunosuppressive regimens when appropriate, and incorporating biomarker-guided monitoring to support precision medicine while reducing treatment-related adverse effects (3). In addition, a better understanding of complement-mediated kidney injury has identified complement inhibition as a promising therapeutic strategy that may further improve disease control and renal preservation in LN(16).

Table no.1 The 2003 ISN/RPS classification of LN(17)

Class	Description
Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN* (<50% of glomeruli) • III (A): active lesions • III (A/C): active and chronic lesions • III (C): chronic lesions
Class IV	Diffuse LN* (≥50% of glomeruli) Diffuse segmental (IV-S) or global (IV-G) LN • IV (A): active lesions • IV (A/C): active and chronic lesions • IV (C): chronic lesions
Class V	Membranous LN
Class VI	Advanced sclerosing LN (≥90% globally sclerosed glomeruli without residual activity)

LN: Lupus nephritis.

1. Indicate the proportion of glomeruli with active and sclerotic lesions.
2. Indicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents.
3. Indicate and grade (mild, moderate , or severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis , and other vascular lesions.
4. Class V may occur in combination with III or IV, in which case both are diagnosed.

1. Advances in Diagnosis of Lupus Nephritis

Early recognition of lupus nephritis is essential to prevent irreversible kidney damage and improve long-term renal outcomes. Kidney biopsy remains the gold standard for confirming the diagnosis, classifying renal lesions, and guiding treatment decisions (3). However, its invasive nature and

limited feasibility for repeated monitoring have prompted the search for reliable non-invasive diagnostic tools (4). Conventional laboratory markers, including proteinuria, serum creatinine, urinary sediment, and complement levels, often lack sufficient sensitivity and specificity for detecting early renal inflammation or accurately reflecting disease activity(2). Consequently, considerable research has focused on identifying novel urinary and circulating biomarkers that enable earlier diagnosis and better monitoring of treatment response (10). More recently, advances in artificial intelligence (AI) and machine learning have shown promise in integrating clinical, laboratory, histopathological, and multi-omics data to improve diagnostic accuracy, predict disease progression, and facilitate personalized management of patients with LN (9).

1.1 Conventional Diagnostic Approaches

Clinical Evaluation

Patients with LN may present with asymptomatic proteinuria, microscopic hematuria, hypertension, nephrotic syndrome, and rapidly progressive glomerulonephritis. Since renal involvement may occur without overt symptoms, routine screening of all patients with SLE using urinalysis, serum creatinine, and urine protein quantification is recommended. The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 guideline advises regular assessment of renal function and urinary abnormalities to facilitate early diagnosis and timely intervention(3).

Urinalysis and Proteinuria Assessment

Urinalysis remains the initial screening tool for detecting renal involvement. Persistent proteinuria (>0.5 g/day or urine protein-to-creatinine ratio [UPCR] ≥0.5 g/g), microscopic hematuria, leukocyturia, and cellular casts are suggestive of active LN. Proteinuria is the most widely used marker for disease activity and therapeutic response. However, proteinuria alone lacks specificity because it may persist despite histological remission due to chronic glomerular damage(6).

The UPCR has largely replaced 24-hour urinary protein estimation because of its convenience, reproducibility, and good correlation with total protein excretion. Reduction in proteinuria during the first 6–12 months of therapy is one of the strongest predictors of long-term renal outcomes (3).

Serum Creatinine and Estimated Glomerular Filtration Rate

Serum creatinine and estimated glomerular filtration rate (eGFR) are routinely used to assess kidney function. However, these parameters are relatively insensitive indicators of early renal injury because significant nephron loss may occur before measurable changes become evident. Consequently, normal serum creatinine levels do not exclude active nephritis, particularly during the early stages of the disease(7).

Autoantibodies

Autoantibody profiling plays a central role in the evaluation of patients with lupus nephritis (LN). Among the various autoantibodies, anti-double-stranded DNA (anti-dsDNA) antibodies are most consistently associated with renal disease activity, and increasing antibody levels often precede the onset of renal flares (2). When accompanied by reduced serum complement concentrations, rising anti-dsDNA titers may indicate an increased risk of disease relapse. However, elevated anti-dsDNA antibody levels alone are not sufficient to diagnose LN, as many patients with positive serology do not

develop clinically significant renal involvement, thereby limiting their diagnostic specificity(8).

Other autoantibodies associated with LN include anti-C1q, anti-nucleosome, and anti-Sm antibodies. Among these, anti-C1q antibodies have shown promising diagnostic performance for predicting proliferative nephritis and renal relapse(9).

Complement Levels

Complement components C3 and C4 are widely used biomarkers of disease activity. During active nephritis, complement consumption leads to decreased serum C3 and C4 concentrations. Persistent hypocomplementemia is associated with severe disease and an increased risk of renal flares. However, complement levels may remain normal in some patients with histologically active disease, highlighting the need for additional biomarkers(3).

Kidney Biopsy

Renal biopsy remains the gold standard for diagnosing LN and determining histological classification according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system. Histological evaluation provides information on disease activity, chronicity, and prognosis, enabling individualized treatment selection. The KDIGO 2024 guidelines recommend kidney biopsy whenever clinically feasible in patients with suspected active LN, particularly before initiating immunosuppressive therapy(3).

Although biopsy provides invaluable diagnostic information, it is invasive, associated with procedural risks, and unsuitable for repeated monitoring. Consequently, considerable research efforts have focused on identifying reliable non-invasive biomarkers capable of replacing repeat biopsies during disease follow-up(5).

1.2 Emerging Biomarkers.

The limitations of conventional laboratory investigations have accelerated the search for biomarkers that accurately reflect ongoing renal inflammation before irreversible structural damage occurs. An ideal biomarker should be non-invasive, highly sensitive, disease-specific, reproducible, and capable of predicting therapeutic response and renal flares (11).

1.2.1 Urinary Biomarkers

Urinary biomarkers directly reflect renal inflammation because they originate from the injured renal tissue.

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is produced by injured tubular epithelial cells and neutrophils during acute kidney injury. Elevated urinary NGAL levels are strongly correlated with active LN, histological activity, and subsequent renal flares. Several studies have demonstrated that NGAL may detect renal inflammation earlier than conventional laboratory parameters(7).

Monocyte Chemoattractant Protein-1 (MCP-1)

MCP-1 is a chemokine that recruits monocytes and macrophages into inflamed renal tissue. Urinary MCP-1 concentrations are closely correlated with disease activity, proteinuria, and histological severity. Elevated MCP-1 levels have also been associated with poor treatment response and increased risk of relapse(13).

Tumor Necrosis Factor-like Weak Inducer of Apoptosis (TWEAK)

Urinary TWEAK promotes inflammation through the activation of the nuclear factor-kappa B signaling pathway. Increased urinary TWEAK concentrations are observed during active nephritis and decline following successful treatment, making it a promising biomarker for monitoring disease activity(14).

Vascular Cell Adhesion Molecule-1 (VCAM-1)

VCAM-1 is expressed on activated endothelial cells and facilitates leukocyte migration into inflamed renal tissue. Elevated urinary VCAM-1 levels have demonstrated excellent correlation with active proliferative nephritis and may predict impending renal flares(15).

Kidney Injury Molecule-1 (KIM-1)

KIM-1 is a sensitive marker of tubular injury that reflects ongoing renal damage before measurable reductions in glomerular filtration are observed. Emerging evidence suggests that urinary KIM-1 may complement conventional biomarkers in monitoring treatment response(12).

1.2.2 Serum Biomarkers

Several circulating biomarkers have been investigated for improving disease monitoring.

- Anti-C1q antibodies are associated with proliferative LN and renal relapses.
- Interleukin-6 (IL-6)levels correlate with inflammatory activity and disease severity.
- Interleukin-17 (IL-17) promotes neutrophil recruitment and glomerular inflammation.
- CXCL13 reflects B cell activation and germinal centre activity.
- BAFF concentrations correlate with autoreactive B-cell survival and therapeutic response to belimumab (3).

Although individually, these biomarkers have limitations, combining multiple biomarkers into diagnostic panels significantly improves diagnostic accuracy.

1.2.3 Molecular Biomarkers and Multi-omics

Recent advances in genomics, transcriptomics, proteomics, metabolomics, and single-cell RNA sequencing have transformed biomarker discovery in LN. Transcriptomic analyses have identified interferon-related gene signatures associated with severe renal disease, whereas proteomic studies have revealed novel urinary proteins capable of detecting subclinical nephritis(16).

Single-cell RNA sequencing has demonstrated marked cellular heterogeneity within renal tissues, identifying distinct inflammatory pathways among individual patients. These findings support the concept of precision medicine, whereby treatment selection is guided by each patient's unique molecular profile rather than conventional clinical parameters alone(18).

Table 2. Emerging Biomarkers in Lupus Nephritis (7)

Biomarker	Sample	Clinical utility
NGAL	Urine	Early kidney injury, disease activity
MCP-1	Urine	Renal inflammation, flare prediction
TWEAK	Urine	Monitoring treatment response
VCAM-1	Urine	Active proliferative nephritis
KIM-1	Urine	Tubular injury
Anti-C1q	Serum	Proliferative nephritis
IL-6	Serum	Disease activity
IL-17	Serum	Inflammatory activity
BAFF	Serum	B-cell activation
CXCL13	Serum	Germinal center activity

1.3 Artificial Intelligence and Precision Medicine

Artificial intelligence (AI) is emerging as a valuable tool in lupus nephritis by integrating clinical, laboratory, imaging, and molecular data to improve the prediction of disease activity, renal flares, and treatment response(19). Precision medicine complements AI by using individual patient characteristics, including biomarkers and genetic profiles, to support personalized therapeutic decisions and improve clinical outcomes(9,19). However, further validation and standardization are required before these approaches can be routinely implemented in clinical practice(19).

AI-assisted Renal Pathology

Digital pathology integrated with deep learning has enhanced the evaluation of renal biopsy specimens by enabling automated detection and quantification of histopathological features such as glomerulosclerosis, interstitial fibrosis, and inflammatory lesions, thereby improving consistency and reducing observer variability in pathological assessment (20).

Prediction of Treatment Response

Machine learning models that integrate clinical characteristics, laboratory parameters, biomarkers, and histopathological findings have shown a promising ability to predict complete renal response following induction therapy. Such predictive models may assist clinicians in selecting individualized therapeutic strategies while minimizing unnecessary exposure to immunosuppressive drugs(21).

Precision Medicine

Precision medicine aims to personalize lupus nephritis treatment by integrating an individual's genetic profile, immune pathways, molecular biomarkers, and clinical phenotype to guide therapeutic decisions(3). Advances in transcriptomic, proteomic, metabolomic, and artificial intelligence–based analytics have improved the identification of patients who are more likely to benefit from targeted therapies, including belimumab, voclosporin, and interferon pathway inhibitors(19). Although these approaches are still evolving and are not routinely used in clinical practice, they represent a promising future direction in the management of lupus nephritis.

Advances in transcriptomic, proteomic, metabolomic, and single-cell RNA sequencing have demonstrated substantial molecular heterogeneity among patients with LN. Molecular profiling enables the identification of distinct inflammatory pathways, facilitating personalized therapeutic selection and prediction of treatment response. Integration of these technologies with artificial intelligence may enable biomarker-guided precision medicine and improve long-term renal outcomes(3).

2. Current Management of Lupus Nephritis

The management of lupus nephritis (LN) has evolved considerably over the past decade owing to advances in the understanding of disease pathogenesis and the introduction of targeted biological therapies. The primary goals of treatment are to achieve complete renal remission, preserve kidney function, prevent disease flares, minimize treatment-related toxicity, and improve long-term survival. Contemporary management follows a treat-to-target approach that combines supportive care with immunosuppressive therapy tailored according to the histological class, disease severity, comorbidities, fertility considerations, and patient preferences(3). The KDIGO 2024, American College of Rheumatology (ACR), and

European Alliance of Associations for Rheumatology (EULAR) guidelines recommend individualized treatment strategies emphasizing early initiation of therapy, reduced glucocorticoid exposure, and incorporation of targeted biologics in appropriate patients(3,22,23).

2.1 General Supportive Therapy

Supportive management is recommended for all patients with LN, regardless of disease class, because it reduces cardiovascular risk, slows chronic kidney disease progression, and improves long-term renal outcomes (3).

Hydroxychloroquine

Hydroxychloroquine (HCQ) remains the cornerstone of SLE management and should be prescribed to nearly all patients with LN, unless contraindicated(3). HCQ exerts immunomodulatory effects by inhibiting lysosomal activity, antigen presentation, and Toll-like receptor signaling, thereby reducing autoantibody production and inflammatory cytokine release. Long-term HCQ therapy is associated with fewer disease flares, improved renal outcomes, reduced thrombotic events, and lower mortality(4). The recommended dose should not exceed 5 mg/kg/day of actual body weight to minimize the risk of retinal toxicity. Regular ophthalmological screening is advised after five years of therapy or earlier in high-risk individuals(3).

Blood Pressure Control

Hypertension accelerates renal damage and increases cardiovascular morbidity in patients with LN. Current guidelines recommend maintaining blood pressure below 130/80 mmHg, preferably using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), particularly in patients with persistent proteinuria(3). Beyond blood pressure reduction, these agents decrease intraglomerular pressure, reduce proteinuria, and slow the progression of chronic kidney disease(6).

Reduction of Proteinuria

Persistent proteinuria is an independent predictor of adverse renal outcomes in patients with IgAN. ACEIs and ARBs should be initiated in patients with proteinuria exceeding 0.5 g/day, provided that renal function and serum potassium levels permit their use(3). Sodium restriction and blood pressure optimization further enhance the antiproteinuric effects. Early reduction in proteinuria during treatment strongly predicts complete renal remission and a favorable long-term prognosis(6).

Lipid Management

Patients with LN have an increased risk of accelerated atherosclerosis due to chronic inflammation, glucocorticoid exposure, and nephrotic syndrome. Statin therapy is recommended according to general cardiovascular risk assessment, particularly in patients with dyslipidemia or chronic kidney disease. Lifestyle interventions, including dietary modification, smoking cessation, and regular physical activity, should also be encouraged(5).

Vaccination and Infection Prevention

Because immunosuppressive therapy increases the risk of serious infections, vaccination status should be assessed before initiating treatment. Inactivated influenza, pneumococcal, hepatitis B, and coronavirus disease (COVID-19) vaccines are recommended as per national guidelines. Live vaccines should generally be avoided during intensive immunosuppression. Screening for latent

tuberculosis, hepatitis B, hepatitis C, and HIV is recommended before initiating biological therapy or cyclophosphamide (3).

Lifestyle Measures

Patients should be advised to avoid excessive ultraviolet light exposure, maintain regular exercise, achieve optimal body weight, ensure adequate calcium and vitamin D intake, and discontinue smoking to prevent osteoporosis. Psychological support and patient education regarding medication adherence, pregnancy planning, and early recognition of disease flares are integral components of comprehensive care(5).

2.2 Induction Therapy

Induction therapy aims to rapidly suppress immune-mediated inflammation, achieve complete or partial renal remission, and prevent irreversible kidney damage in patients with AAV. Treatment selection depends primarily on the histological class of LN, disease severity, fertility considerations, ethnicity, comorbidities, and patient preference(3).

Mycophenolate Mofetil (MMF)

Mycophenolate mofetil (MMF) is recommended as a first-line induction therapy for patients with Class III, Class IV, and Class V lupus nephritis(3).MMF selectively inhibits inosine monophosphate dehydrogenase, resulting in suppression of T- and B-lymphocyte proliferation and reduced autoantibody production. Clinical evidence has shown that MMF provides renal outcomes comparable to cyclophosphamide while being associated with a lower risk of gonadal toxicity and serious infections. It has demonstrated particularly favorable outcomes in Asian and African populations(8). During induction therapy, MMF is generally administered at a dose of 2–3 g/day in combination with glucocorticoids(3).

Cyclophosphamide

Cyclophosphamide remains an effective induction agent, especially in patients with severe proliferative LN, rapidly progressive glomerulonephritis, and poor prognostic features. The Euro-Lupus regimen (500 mg intravenously every two weeks for six doses) has demonstrated efficacy comparable to that of high-dose regimens while substantially reducing cumulative toxicity, infertility, and malignancy risk. High-dose cyclophosphamide may still be preferred in selected patients with aggressive disease or inadequate response to alternative therapies(9).

Glucocorticoids

Glucocorticoids remain an essential component of induction therapy because of their rapid anti-inflammatory effects. Recent guidelines advocate lower cumulative steroid exposure to reduce long-term complications such as diabetes mellitus, osteoporosis, infections, cataracts, and cardiovascular disease. Intravenous methylprednisolone pulses (250–500 mg daily for 1–3 days) followed by oral prednisone (approximately 0.35–0.5 mg/kg/day) with gradual tapering are recommended for most patients(3).

Triple Immunosuppressive Therapy

One of the most significant changes introduced in the KDIGO 2024 and ACR 2024/2025 recommendations is the incorporation of triple immunosuppressive therapy in patients with active proliferative LN. Triple therapy combines glucocorticoids with MMF and either belimumab or voclosporin, improving the complete renal response while allowing earlier glucocorticoid reduction. This approach has demonstrated

superior efficacy compared to conventional dual therapy in recent clinical trials(3).

2.3 Maintenance Therapy

Maintenance therapy aims to sustain remission, prevent renal relapse, minimize cumulative glucocorticoid exposure, and preserve long-term kidney function. Treatment is generally continued for at least 36 months, although the duration should be individualized according to disease activity and relapse risk3 (3).

Mycophenolate Mofetil

MMF is the preferred maintenance agent because it significantly reduces renal relapse compared with azathioprine in several randomized trials. Maintenance doses typically range from 1–2 g/day and are adjusted according to renal response and tolerability(11).

Azathioprine

Azathioprine remains an alternative maintenance therapy, particularly in women planning pregnancy, because of its favorable fetal safety profile compared with MMF. Although effective, azathioprine is associated with higher relapse rates than MMF and is therefore generally reserved for selected patients or those intolerant to MMF(11).

Calcineurin Inhibitors

Tacrolimus and voclosporin may also be used during maintenance therapy, particularly in patients with persistent proteinuria or inadequate responses to conventional therapy. These agents stabilize podocyte function, reduce proteinuria, and exert additional immunosuppressive effects. However, long-term monitoring is required because of potential nephrotoxicity and hypertension(7).

Glucocorticoid Tapering

Recent guidelines strongly emphasize the need to minimize glucocorticoid exposure. Prednisone should be tapered gradually to ≤5 mg/day whenever clinically feasible, with complete discontinuation considered in patients who achieve sustained remission. Reduced glucocorticoid exposure decreases cumulative toxicity without compromising renal outcomes when combined with effective immunosuppressive therapy(3).

Monitoring During Therapy

Patients receiving immunosuppressive therapy require regular monitoring of renal function, urine protein excretion, complete blood count, liver function tests, serum complement levels, anti-dsDNA antibody titers, and adverse drug reactions. Therapeutic monitoring facilitates the early identification of disease flares, drug toxicity, and treatment failure(3). Biomarker-guided monitoring using urinary NGAL, MCP-1, and TWEAK is increasingly being investigated but has not yet been incorporated into routine clinical practice(13).

3. Recent Therapeutic Advances

The therapeutic landscape of lupus nephritis (LN) has undergone a paradigm shift with the introduction of targeted biologic agents and novel immunomodulatory therapies3 (3). While conventional induction regimens comprising glucocorticoids, mycophenolate mofetil (MMF), and cyclophosphamide remain effective, a considerable proportion of patients fail to achieve complete renal remission or experience frequent relapses24 (24). Advances in the understanding of the immunopathogenesis of LN have facilitated the development of therapies targeting B cells, cytokines, complement pathways, and interferon

signalling (2). These targeted agents have demonstrated improved renal response rates, reduced disease activity, and the potential to minimise glucocorticoid exposure.

3.1 Belimumab

Belimumab is a fully human monoclonal antibody directed against soluble B-lymphocyte stimulator (BLyS), also known as B-cell activating factor (BAFF). BAFF plays a crucial role in the survival, maturation, and differentiation of autoreactive B lymphocytes. Elevated BAFF levels in patients with SLE promote the persistence of autoreactive B cells and increased production of pathogenic autoantibodies. By inhibiting BAFF, belimumab reduces autoantibody production, attenuates immune complex formation, and decreases inflammatory activity(6).

The landmark BLISS-LN trial established the efficacy of belimumab in LN, a phase III randomized controlled study involving patients with active Class III, IV, and V LN receiving standard therapy with MMF or cyclophosphamide. Patients treated with belimumab plus standard therapy achieved significantly higher primary efficacy renal response and complete renal response at two years compared with those receiving placebo. Additionally, belimumab reduced renal flares and improved long-term renal outcomes without a significant increase in serious adverse events(13).

Based on these findings, the KDIGO 2024, ACR 2024, and EULAR recommendations endorse belimumab as part of triple immunosuppressive therapy for patients with active proliferative LN who are at high risk of disease progression or relapse(3).The most frequently reported adverse effects include infusion-related reactions, upper respiratory tract infections, nausea, diarrhoea, and headache. Overall, belimumab has an acceptable safety profile and is generally well tolerated(4).

3.2 Voclosporin

Voclosporin is a novel oral calcineurin inhibitor structurally related to cyclosporine but modified to provide greater pharmacokinetic stability and reduced interpatient variability(3). Like other calcineurin inhibitors, voclosporin inhibits calcineurin phosphatase activity, preventing the activation of nuclear factor of activated T cells (NFAT) and subsequent T-cell activation. Additionally, it stabilizes podocyte cytoskeletal architecture, thereby reducing proteinuria independently of its immunosuppressive effects(4).

The AURORA-1 trial demonstrated that voclosporin combined with MMF and low-dose glucocorticoids produced significantly higher complete renal response rates at 52 weeks than standard therapy alone. Patients receiving voclosporin also experienced earlier reductions in proteinuria while maintaining acceptable safety profiles(14). Long-term follow-up from the AURORA-2 extension study confirmed sustained renal efficacy and favourable safety over three years(25).

Consequently, voclosporin has become an important component of triple immunosuppressive therapy for active proliferative LN. Careful monitoring of renal function, blood pressure, and serum potassium levels is recommended during treatment because calcineurin inhibitors may cause nephrotoxicity and hypertension(3).

3.3 Rituximab

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen expressed on mature B lymphocytes. Depletion of CD20-

positive B cells reduces autoantibody production, antigen presentation, and cytokine secretion, thereby suppressing autoimmune activity. Although the LUNAR trial did not demonstrate a statistically significant improvement in primary renal outcomes with the addition of rituximab to standard therapy, several observational studies and real-world cohorts have reported favourable responses in refractory or relapsing LN (9).

The RITUXILUP study further suggested that rituximab combined with MMF and minimal glucocorticoid exposure may induce remission while reducing steroid-related adverse effects(26). Consequently, current guidelines reserve rituximab for patients with refractory disease, intolerance to conventional immunosuppressive therapy, or recurrent LN despite optimised treatment(3).

The common adverse effects of rituximab include infusion reactions, hypogammaglobulinemia, hepatitis B reactivation, and opportunistic infections. Screening for hepatitis B virus infection before treatment initiation is strongly recommended(3).

3.4 Obinutuzumab

Obinutuzumab is a humanized type II anti-CD20 monoclonal antibody that produces more potent and sustained B-cell depletion than rituximab through enhanced antibody-dependent cellular cytotoxicity and direct cell death(11).

The phase II NOBILITY trial demonstrated significantly higher complete renal response rates among patients receiving obinutuzumab plus standard therapy compared to placebo(27). More recently, the phase III REGENCY trial confirmed superior renal responses and sustained B-cell depletion with obinutuzumab in proliferative LN. These encouraging findings suggest that obinutuzumab may become an important therapeutic option for patients with active LN in future clinical practice(15).

Overall, obinutuzumab demonstrated acceptable tolerability, with infusion-related reactions and infections representing the most common adverse events.

3.5 Anifrolumab

Anifrolumab is a fully human monoclonal antibody that targets type I interferon receptor subunit 1 (IFNAR1), thereby blocking signalling through the type I interferon pathway. Persistent activation of the type I interferon pathway promotes activation of dendritic cells, B cells, T cells, and innate immune responses and is associated with increased disease activity and renal involvement in systemic lupus erythematosus(6). The TULIP-1 and TULIP-2 phase III trials demonstrated the efficacy of anifrolumab in patients with moderate-to-severe systemic lupus erythematosus receiving standard therapy. A phase II study in patients with active lupus nephritis showed that intensified anifrolumab treatment improved renal response and reduced proteinuria, although further phase III studies are needed before routine incorporation into lupus nephritis treatment guidelines. The most commonly reported adverse effects include upper respiratory tract infections, herpes zoster, bronchitis, and infusion-related reactions(28). The KDIGO 2024 Clinical Practice Guideline considers anifrolumab an emerging therapy for lupus nephritis, with its role expected to expand as additional clinical evidence becomes available(3).

3.6 Emerging Biological Therapies

Several novel therapies targeting distinct immune pathways are currently being clinically evaluated.

Complement Inhibitors

Excessive complement activation contributes substantially to renal inflammation in LN. Therapeutic agents targeting complement components, such as C5, factor B, and the C5a receptor, are being investigated to interrupt complement-mediated tissue injury. Preliminary studies have demonstrated encouraging reductions in inflammatory activity; however, further evidence is required before routine clinical use(22).

Plasma Cell-Targeted Therapy

Long-lived plasma cells continue to produce pathogenic autoantibodies despite conventional B-cell depletion. Monoclonal antibodies targeting CD38, including daratumumab, are currently being investigated in refractory SLE and LN with promising preliminary results(3).

Chimeric Antigen Receptor (CAR)-T Cell Therapy

Autologous CAR-T cell therapy directed against CD19-positive B cells has emerged as a novel therapeutic approach for severe refractory autoimmune diseases. Early clinical studies have demonstrated prolonged drug-free remission in patients with treatment-resistant SLE, suggesting potential applicability to severe LN. However, larger clinical trials are necessary to establish long-term efficacy and safety(16).

Stem Cell Therapy

Mesenchymal stem cells exhibit immunomodulatory properties by suppressing autoreactive lymphocytes and promoting immune tolerance. Although preliminary studies have demonstrated improvements in refractory LN, standardized protocols and long-term safety data remain limited(18).

4. Comparison of Current International Guidelines

The management of lupus nephritis (LN) has been significantly refined by recent updates from the Kidney Disease: Improving Global Outcomes (KDIGO) 2024, American College of Rheumatology (ACR) 2024/2025, and European Alliance of Associations for Rheumatology (EULAR) guidelines. Although all three guidelines emphasize early diagnosis, prompt kidney biopsy, individualized immunosuppressive therapy, and long-term monitoring, differences exist in their recommendations regarding induction therapy, biological therapy, and glucocorticoid tapering (3,23,24).

The KDIGO 2024 guidelines recommend kidney biopsy for all patients with suspected active LN whenever feasible. For patients with Class III or IV LN, induction therapy consists of glucocorticoids combined with mycophenolate mofetil (MMF) or low-dose intravenous cyclophosphamide. The guideline also supports the addition of belimumab or voclosporin as part of triple immunosuppressive therapy in selected patients with severe disease or high relapse risk. Furthermore, KDIGO emphasizes minimizing glucocorticoid exposure by adopting lower starting doses and rapid tapering schedules(3).

The ACR 2024/2025 recommendations similarly advocate early kidney biopsy but place greater emphasis on upfront triple therapy, particularly MMF combined with glucocorticoids and either belimumab or voclosporin. The ACR recommendations encourage shared decision-making, individualized treatment selection based on patient characteristics, and regular assessment of treatment response using proteinuria and renal function(23).

The EULAR recommendations continue to support MMF and low-dose cyclophosphamide as first-line induction therapies while acknowledging the growing role of biologic agents. EULAR also emphasizes hydroxychloroquine use in all patients, unless contraindicated, cardiovascular risk reduction, infection prevention, and multidisciplinary management involving rheumatologists, nephrologists, pharmacists, and specialist nurses(24).

Despite minor differences, all three guidelines promote a treat-to-target strategy focusing on early remission, reduced glucocorticoid exposure, individualized therapy, and prevention of CKD progression.

Table No. 3: Comparison of guidelines (3,23,24)

Aspect	KDIGO 2024	ACR 2024/ 2025	EULAR
Kidney biopsy	Recommended whenever feasible	Recommended	Recommended
First-line induction	MMF or low-dose cyclophosphamide	MMF-based triple therapy preferred	MMF or cyclophosphamide
Belimumab	Recommended	Recommended	Recommended
Voclosporin	Recommended	Recommended	Consider in selected patients
Hydroxychloroquine	Recommended for all	Recommended for all	Recommended for all
Glucocorticoids	Lower dose and rapid taper	Early taper strongly encouraged	Minimize steroid exposure
Maintenance	MMF preferred	MMF preferred	MMF preferred

5. Future Directions

Remarkable advances in immunology and molecular medicine have accelerated the transition from conventional immunosuppression to personalized management of LN. Future research is expected to focus on biomarker-guided therapy, precision medicine, artificial intelligence (AI), and novel targeted therapies that improve long-term renal outcomes while minimizing treatment-related toxicity (4).

Precision Medicine

Precision medicine seeks to individualize treatment according to each patient's molecular profile rather than relying solely on histological classification. Advances in transcriptomic, proteomic, and metabolomic analyses, as well as single-cell RNA sequencing, have identified distinct immune signatures that may predict therapeutic response. Such molecular stratification may allow clinicians to select the most appropriate biologic therapy for individual patients, thereby improving efficacy and reducing unnecessary exposure to ineffective treatments(6).

Artificial Intelligence

AI has emerged as a promising tool for improving the diagnosis, prognosis, and therapeutic decision-making in LN. Machine learning algorithms integrating demographic, laboratory, histopathological, and biomarker data have demonstrated encouraging accuracy in predicting renal flares, treatment response, and disease progression. AI-assisted digital pathology may further improve the reproducibility of kidney biopsy interpretation and facilitate standardized disease classification(5).

Novel Biomarkers

Future studies are expected to validate urinary biomarkers, including NGAL, MCP-1, TWEAK, VCAM-1, KIM-1, and multi-biomarker panels, for routine clinical practice. Integration of biomarker panels with conventional laboratory investigations may permit earlier diagnosis, better disease monitoring, and timely therapeutic adjustment before irreversible renal injury occurs(7)

Emerging Therapeutic Targets

Several innovative therapeutic approaches are under active investigation. Complement inhibitors targeting C5 and factor B, anti-CD38 antibodies, Bruton tyrosine kinase inhibitors, Janus kinase inhibitors, plasma cell-directed therapies, mesenchymal stem cell transplantation, and chimeric antigen receptor (CAR)-T cell therapy have demonstrated promising preliminary results. Continued evaluation in large randomized clinical trials will determine their future role in LN management(8).

CONCLUSION

Lupus nephritis remains one of the most severe manifestations of systemic lupus erythematosus and continues to be a major cause of chronic kidney disease and end-stage kidney disease worldwide. Early diagnosis, prompt kidney biopsy, and timely initiation of immunosuppressive therapy remain fundamental to preserving renal function and improving patient survival. Recent advances in understanding disease pathogenesis have facilitated the development of targeted biological therapies, including belimumab and voclosporin, which have significantly improved renal response rates and reduced disease flares when combined with conventional immunosuppressive agents.

The emergence of urinary biomarkers, molecular profiling, artificial intelligence, and precision medicine has the potential to transform the diagnosis and monitoring of LN by enabling individualized therapeutic strategies for patients with LN. Contemporary international guidelines from KDIGO, ACR, and EULAR increasingly emphasize reduced glucocorticoid exposure, combination immunosuppressive therapy, and personalized management based on disease severity and patient characteristics.

Although substantial progress has been achieved, important challenges remain regarding the prediction of treatment response, prevention of relapse, and optimization of long-term renal outcomes. Future research focusing on biomarker-guided treatment, novel biologic agents, and precision nephrology is expected to further improve the management of LN and enhance the quality of life of affected patients.

REFERENCES

1. Hoi A, Igel T, Mok CC, Arnaud L. Systemic lupus erythematosus. The Lancet. 2024 May;403(10441):2326–38. doi:10.1016/S0140-6736(24)00398-2
2. Almaani S, Meara A, Rovin BH. Update on Lupus Nephritis. Clin J Am Soc Nephrol. 2017 May;12(5):825–35. doi:10.2215/CJN.05780616
3. Rovin BH, Ayoub IM, Chan TM, Liu ZH, Mejía-Vilet JM, Floege J. KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. Kidney Int. 2024 Jan;105(1):S1–69. doi:10.1016/j.kint.2023.09.002
4. Parikh SV, Almaani S, Brodsky S, Rovin BH. Update on Lupus Nephritis: Core Curriculum 2020. Am J Kidney Dis. 2020 Aug;76(2):265–81. doi:10.1053/j.ajkd.2019.10.017
5. Tsokos GC, Lo MS, Reis PC, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol. 2016 Dec;12(12):716–30. doi:10.1038/nrrheum.2016.186

6. Anders HJ, Saxena R, Zhao M Hui, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nat Rev Dis Primer. 2020 Jan 23;6(1):7. doi:10.1038/s41572-019-0141-9
7. Vrabie A, Obrișcă B, Sorohan BM, Ismail G. Biomarkers in Lupus Nephritis: An Evidence-Based Comprehensive Review. Life. 2025 Sep 23;15(10):1497. doi:10.3390/life15101497 PubMed PMID: 41157170; PubMed Central PMCID: PMC12565261.
8. Sharafaldin ENK, Sim MS, Lim SK, Alhussieni K, Huri HZ. Precision medicine in lupus nephritis. Clin Chim Acta. 2024 Aug 15;562:119894. doi:10.1016/j.cca.2024.119894
9. Parodis I, Tamirou F, Houssiau FA. Prediction of prognosis and renal outcome in lupus nephritis. Lupus Sci Med. 2020 Feb;7(1):e000389. doi:10.1136/lupus-2020-000389
10. Omer MH, Shafqat A, Ahmad O, Nadri J, AlKattan K, Yaqinuddin A. Urinary Biomarkers for Lupus Nephritis: A Systems Biology Approach. J Clin Med. 2024 Jan;13(8):2339. doi:10.3390/jcm13082339
11. Li Y, Tang C, Vanarsa K, Thai N, Castillo J, Lea GAB, et al. Proximity extension assay proteomics and renal single-cell transcriptomics uncover novel urinary biomarkers for active lupus nephritis. J Autoimmun. 2024 Feb 1;143:103165. doi:10.1016/j.jaut.2023.103165
12. Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis. 2021 Jan;80(1):14–25. doi:10.1136/annrheumdis-2020-218272
13. Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020 Sep 17;383(12):1117–28. doi:10.1056/NEJMoa2001180
14. Rovin BH, Teng YKO, Ginzler EM, Arriens C, Caster DJ, Romero-Diaz J, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomized, multicenter, placebo-controlled, phase 3 trial. The Lancet. 2021 May 29;397(10289):2070–80. doi:10.1016/S0140-6736(21)00578-X PubMed PMID: 33971155.
15. Furie RA, Dall'Era M, Vital EM, Garg JP, Palazuelos FI, Santillán AEZ, et al. Efficacy and Safety of Obinutuzumab in Active Systemic Lupus Erythematosus. N Engl J Med. 0(0). doi:10.1056/NEJMoa2516150
16. Satyam A, Hisada R, Bhargava R, Tsokos MG, Tsokos GC. Intertwined pathways of complement activation command the pathogenesis of lupus nephritis. Transl Res J Lab Clin Med. 2022 Jul;245:18–29. doi:10.1016/j.trsl.2022.03.005 PubMed PMID: 35296451; PubMed Central PMCID: PMC9167748.
17. Markowitz GS, D'Agati VD. The ISN/RPS 2003 classification of lupus nephritis: An assessment at 3 years. Kidney Int. 2007 Mar 2;71(6):491–5. doi:10.1038/sj.ki.5002118 PubMed PMID: 17264872.
18. Wigerblad G, Kaplan MJ. Neutrophil extracellular traps in systemic autoimmune and autoinflammatory diseases. Nat Rev Immunol. 2023 May;23(5):274–88. doi:10.1038/s41577-022-00787-0
19. Shang S, Xia J, He G, Zheng Y, Zhang J, Lu H, et al. Advances in precision medicine for lupus nephritis: biomarker- and AI-driven diagnosis and treatment response prediction and targeted therapies. eBioMedicine. 2025 Jun 3;117:105785. doi:10.1016/j.ebiom.2025.105785 PubMed PMID: 40466435; PubMed Central PMCID: PMC12167120.
20. Zheng Z, Zhang X, Ding J, Zhang D, Cui J, Fu X, et al. Deep Learning-Based Artificial Intelligence System for Automatic Assessment of Glomerular Pathological Findings in Lupus Nephritis. Diagnostics. 2021 Oct 26;11(11):1983. doi:10.3390/diagnostics11111983 PubMed PMID: 34829330; PubMed Central PMCID: PMC8621095.
21. Hahn BH, McMahon M, Wilkinson A, Wallace WD, Daikh DI, FitzGerald J, et al.

American College of Rheumatology Guidelines for Screening, Case Definition, Treatment, and Management of Lupus Nephritis. Arthritis Care Res. 2012 Jun;64(6):797–808. doi:10.1002/acr.21664 PubMed PMID: 22556106; PubMed Central PMCID: PMC3437757.

22. Fanouriakis A, Kostopoulou M, Andersen J, Aringer M, Arnaud L, Bae SC, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis. 2024 Jan 2;83(1):15–29. doi:10.1136/ard-2023-224762 PubMed PMID: 37827694.
23. 2024 American College of Rheumatology (ACR) Guidelines for the Screening, Treatment, and Management of Lupus Nephritis [Internet]. doi:10.1002/art.43212
24. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis. 2019 Jun 1;78(6):736–45. doi:10.1136/annrheumdis-2019-215089 PubMed PMID: 30926722.
25. Safety and Efficacy of Long-Term Voclosporin Treatment for Lupus Nephritis in the Phase 3 AURORA 2 Clinical Trial [Internet]. [cited 2026 Jul 18]. Available from: https://acrjournals.onlinelibrary.wiley.com/doi/epdf/10.1002/art.42657 doi:10.1002/art.42657
26. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The lupus nephritis assessment with rituximab study. Arthritis Rheum. 2012;64(4):1215–26. doi:10.1002/art.34359
27. Furie RA, Aroca G, Cascino MD, Garg JP, Rovin BH, Alvarez A, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomized, double-blind, placebo-controlled trial. Ann Rheum Dis. 2022 Jan 1;81(1):100–7. doi:10.1136/annrheumdis-2021-220920 PubMed PMID: 34615636.
28. Jayne D, Rovin B, Mysler EF, Furie RA, Houssiau FA, Trasieva T, et al. Phase II randomized trial of type I interferon inhibitor anifrolumab in patients with active lupus nephritis. Ann Rheum Dis. 2022 Apr 1;81(4):496–506. doi:10.1136/annrheumdis-2021-221478 PubMed PMID: 35144924.

HOW TO CITE: Saja N, Sajitha G, Recent Advances in the Diagnosis and Management of Lupus Nephritis in Systemic Lupus Erythematosus, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 6204-6220. https://doi.org/10.5281/zenodo.21727270