About the Author

Christine A. Peschken, MD, MSc, FRCPC

Dr. Peschken is a Professor of Medicine and Clinician Investigator at the University of Manitoba, focusing on systemic lupus erythematosus. Her main clinical and research focus is systemic lupus erythematosus. Her current research interests include lupus outcomes in vulnerable populations and on systemic lupus and rheumatic disease in Indigenous people. She is currently Chair of the Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus.

Affiliations: Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB
Professor of Medicine and Community Health Sciences, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB

Update on Lupus Nephritis

Christine A. Peschken, MD, MSc, FRCPC

Abstract

Lupus Nephritis (LN) is a common and severe manifestation of systemic lupus erythematosus (SLE), impacting up to 40% of SLE patients. Despite advancements in understanding the pathogenesis of LN, outcomes have not significantly improved since the early 2000s. LN patients face higher mortality, emphasizing the importance of achieving disease remission. Screening for nephritis involves regular monitoring, especially within the first 5 years of SLE diagnosis. Monitoring includes urinalysis, serum creatinine, and immune serology. Kidney biopsy remains the gold standard for LN diagnosis and classification, providing crucial information for treatment decisions. The standard of care involves hydroxychloroquine for all LN patients, with immunosuppressive treatments tailored to the histologic class. The recently approved medications, belimumab and voclosporin, offer additional therapeutic alternatives. Approximately 20% of LN patients exhibit features of thrombotic microangiopathy, warranting anticoagulation. Optimizing glucocorticoid dosing is recommended, favouring lower doses to minimize adverse effects. Lifelong monitoring is essential, as flares can occur at any point, emphasizing the need for continued immunosuppression.

Given the lack of renal response in 30–60% of patients, the addition of combination therapies, such as calcineurin inhibitors or belimumab, should be considered. Duration of treatment is crucial, considering the progressive loss of podocytes and nephron function, which may lead to chronic kidney disease. Regular monitoring, maintenance immunosuppression, and lifestyle modifications contribute to preventing flares and improving long-term outcomes for LN patients.

Introduction

LN is a severe and relatively common manifestation of systemic lupus erythematosus (SLE), affecting as many as 40% of SLE patients, with marked ethnic variations.[1] Approximately 10% of LN patients progress to end stage kidney disease (ESKD) within 10 years of diagnosis,[2] with higher rates for International Society of Nephrology (ISN) Class IV LN, reported at up to 44% progression at 15 years.[3] Patients with LN also have higher mortality; one large study of an inception cohort of 1827 new SLE patients showed an adjusted hazard ratio of death at 10 years of 3.2 for patients with LN versus those without LN.[4] Is important to note that mortality improves substantially if disease remission is achieved.[5]

Although our understanding of the pathogenesis of LN has improved, these outcomes have not improved substantially since approximately 2000. The Euro-Lupus trial, published in 2002, demonstrated the effectiveness of low-dose intravenous cyclophosphamide treatment for proliferative nephritis.[6] In 2009, the Aspreva Lupus Management Study showed no difference in remission induction between mycophenolate and monthly intravenous cyclophosphamide.[7] The ensuing changes in the LN treatment paradigm resulted in reduced treatment related adverse events but did not improve remission rates. For many patients with LN, a complete renal response, and even a partial response, remains elusive. The recent approval of two new medications for LN, with several more promising options in the pipeline, has reinvigorated the discussion on management of LN.

Screening Systemic Lupus Erythematosus Patients for Nephritis

LN can occur at any time during the patient's disease course; however, the highest risk is during the first 5 years after diagnosis. Early diagnosis of LN can improve outcomes. Patients should also be educated about the symptoms of LN, such as general malaise, hypertension, and edema. Thus, screening and monitoring for LN should continue throughout SLE, but should be performed more frequently, ideally every 3 to 6 months for the first 5 years after diagnosis and at least annually thereafter. Screening is completed through a number of tests, including urinalysis, serum creatinine, spot urine protein/creatinine ratio (uPCR) or albumin/creatinine ratio (uACR) and immune serology (dsDNA and complement levels).[8]

Kidney Biopsy

Traditional biomarkers that are used to assess lupus activity include complement levels (C3, C4), anti-dsDNA antibody levels, hematuria, proteinuria, and serum creatinine, including screening for LN as mentioned above, often do not correlate well with activity or diagnosis on kidney biopsy. Despite longstanding attempts to find serum or urine biomarkers to replace kidney biopsy, none have been validated or shown to be of adequate specificity and sensitivity. Kidney biopsy remains the gold standard for diagnosis, histological classification, and assessment of the severity of LN.[2,9]

Referral for biopsy should be considered if the patient experiences an abnormal or sustained reduction in the estimated glomerular filtration rate (eGFR), persistent and significantly elevated proteinuria (≥500 mg/day) and/or urinalysis with persistent proteinuria or hematuria that cannot be explained by an alternate etiology. A multidisciplinary approach including rheumatology and nephrology is recommended.[8,10]

LN is grouped into six histological classes based on the type of glomerular lesions observed[11] **(Table 1)**. In addition to determining the histologic class, and confirming the diagnosis of LN, kidney biopsy can help to determine activity and chronicity. Alternative diagnoses can be confirmed or ruled out, and additional features that influence the prognosis of LN can be determined, such as thrombotic microangiopathy, podocytopathy, and tubulointerstitial lesions. These biopsy findings will help to determine the appropriate monitoring and treatment.[10]

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis (< 50% of glomeruli)
Class IV	Diffuse proliferative lupus nephritis (≥50% of glomeruli)
Class V	Membranous lupus nephritis*
Class VI	Advanced sclerosing lupus nephritis (≥90% of glomeruli globally sclerosis without residual activity)

Table 1: Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of Lupus Nephritis; courtesy of Christine A. Peschken, MD, MSc, FRCPC
*Class V may occur in combination with class III or IV, in which case both will be diagnosed Indicate and grade (mild, moderate, severe tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

It is important to note that the lack of a biopsy should not substantially delay LN treatment. If a biopsy cannot be obtained in a timely fashion, or is contraindicated, consideration should be given for initiating treatment for LN in SLE patients who have convincing signs and symptoms of LN such as a decline in eGFR, persistent proteinuria >500 mg/day, hematuria on urinalysis, and the absence of an alternative explanation.

Standard of Care Treatment

All patients with LN should be treated with hydroxychloroquine unless there are contraindications. Hydroxychloroquine has been shown to improve LN outcomes, reduce LN flares, and delay progression to ESKD.[12]

Immunosuppressive treatment for LN depends on the histologic class and other biopsy features in addition to non-renal lupus activity. Class I and II LN may or may not require immunosuppressive treatment; this is based on levels of proteinuria and/or eGFR as well as other symptoms of lupus.

For Class III or IV LN, with or without a component of membranous nephritis (Class V), the standard of care (SoC) induction therapy includes mycophenolate or low dose intravenous cyclophosphamide, combined with high dose glucocorticoids (see previous page).[13,14] The choice of mycophenolate versus low dose cyclophosphamide is guided by individualized patient and physician discussions. High dose monthly intravenous cyclophosphamide (0.5–1 mg/m^2 body surface area) can be considered for those patients who are at high risk for renal failure (defined as a reduced eGFR, the histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation), or for those with life-threatening disease.[14]

Data remain limited on the treatment of isolated Class V LN. Treatment choices will depend on the level of proteinuria and associated symptoms. For those patients requiring treatment, mycophenolate mofetil is recommended at the same doses as in Class III/IV disease, with calcineurin inhibitors, (particularly tacrolimus) either alone or in combination with mycophenolate mofetil as recommended alternatives.[10]

Class VI LN does not respond to immunosuppression; thus, treatment includes kidney replacement therapy.

Following treatment initiation, patients should be monitored every one to two months for renal response and adverse effects. Treatment targets include a reduction in proteinuria of ≥25% at 3 months and ≥50% at 6 months respectively, and below a level of 500–700 mg/day at 12 months, all while maintaining the eGFR within 10% from baseline.[14] For those not achieving these responses, treatment with the alternative SoC therapy (cyclophosphamide or mycophenolate) should be considered. High dose intravenous cyclophosphamide can also be considered. Combination therapy with belimumab, or calcineurin inhibitors (CNIs) should also be considered if they were not initiated earlier (see previous page). Rituximab can also be considered for refractory disease.[14] Some crucial factors should be considered prior to changing therapy, including adherence to therapy, adequate dosing, and alternative pathology. A repeat renal biopsy may be indicated. Multidisciplinary care with involvement of nephrology is recommended.

New and Additive Treatments

Recent studies have shown that 30% to 60% of patients fail to achieve either a complete or partial renal response. This represents a substantial unmet need in the treatment of LN. The approval of belimumab and voclosporin specifically for LN, after more than 20 years without new therapies, represents an important advance in the field. At the time of writing, belimumab has been approved in Canada, although its access remains limited, and voclosporin has not yet received Health Canada approval. However, there is optimism that access to new and upcoming treatments will improve and it is worthwhile to review their place in the treatment paradigm.

> ***All patients with LN should be treated with hydroxychloroquine unless there are contraindications.***

Voclosporin is more potent than cyclosporine and may cause less hypertension and hyperlipidemia compared to cyclosporine, and may cause less diabetes compared to tacrolimus. Voclosporin has not, however, been directly compared to either of these medications. In phase 3 trials, voclosporin, along with mycophenolate and oral corticosteroids, was shown to significantly improve renal response rates at 52 weeks. These results add to the encouraging literature on CNIs

for treating LN. Tacrolimus as monotherapy, or in combination with mycophenolate, has been shown effective in LN, and the combination has been shown to be superior to intravenous cyclophosphamide for induction therapy in the treatment of LN.[13,14] In the phase 3 LN study that evaluated belimumab, patients received belimumab on a background of SoC therapy. The study demonstrated that a significantly greater number of patients achieved both complete and partial renal response compared to placebo. Flare rates were also reduced, as was the risk of a renal-related event or death.[2]

Addition of a CNI (tacrolimus) to SoC therapy may be a good choice for patients with high levels of proteinuria, and relatively preserved renal function (eGFR >45 mL/min), while the addition of belimumab may be a good choice for patients with severe disease, at high risk of flare or relapse, and for those with a lower eGFR. Neither voclosporin nor belimumab have shown a clear benefit for Class V LN.[15]

While access to and cost of medications, adverse effects, and medication burden are all important and may influence therapeutic decisions, the significant number of patients who do not achieve renal response with SoC therapy suggests that the addition of combination therapy could be actively considered for all LN patients at the onset of treatment. If not added at the onset, failure to meet treatment targets at three months could prompt the addition of combination therapy.

Glucocorticoid Dosing in Lupus Nephritis

The recently updated and published EULAR recommendations for the management of SLE/LN support the use of lower doses of glucocorticoids, as did the 2019 EULAR guidelines for LN.[13,14] Glucocorticoids have both genomic and non-genomic effects. The genomic effects depend on intracellular receptors and alter the expression of pro-inflammatory and immunoregulatory genes. Glucocorticoid receptors are almost fully saturated at an approximately 30 mg/day prednisone equivalent. Higher doses result in further immunosuppression through non-genomic effects. These mechanisms support the suggested strategy of short-term high dose methylprednisolone followed by more moderate doses of oral prednisone.[15]

Pulses of intravenous methylprednisolone are recommended as part of the induction treatment for LN, unless there are concerns for

Treatment of LN Traditional	Drugs	Trends
Steroid pulse	• Steroid pulse • Oral prednisone 1 mg/kg	• May or may not be necessary • Dose and number of days may vary • Trend is less dose and more rapid taper
Hydroxychloroquine	5mg/kg/day	Adjust for some comorbidities
Immune suppression	MMF (i.e. 3g/day) or cyclophosphamide (i.e. 500 mg IV Q2w x 6 doses)	Consider MMF initially for many patients due to equal benefit and more safety
Added immune suppression	Belimumab CNI Other (other drugs in RCTs)	Trend is to consider upfront addition of one of these drugs to MMF or cyclophosphamide vs. Add if an outcome is not achieved at a specific time
Special circumstances	Pregnancy – use azathioprine and consider planning conception only when patient is under excellent control	Consider use of a SGLT2 inhibitors (gliflozins or flozins) for renal protection

Table 2. Trends in the approach to LN tretament; courtesy of Christine A. Peschken, MD, MSc, FRCPC

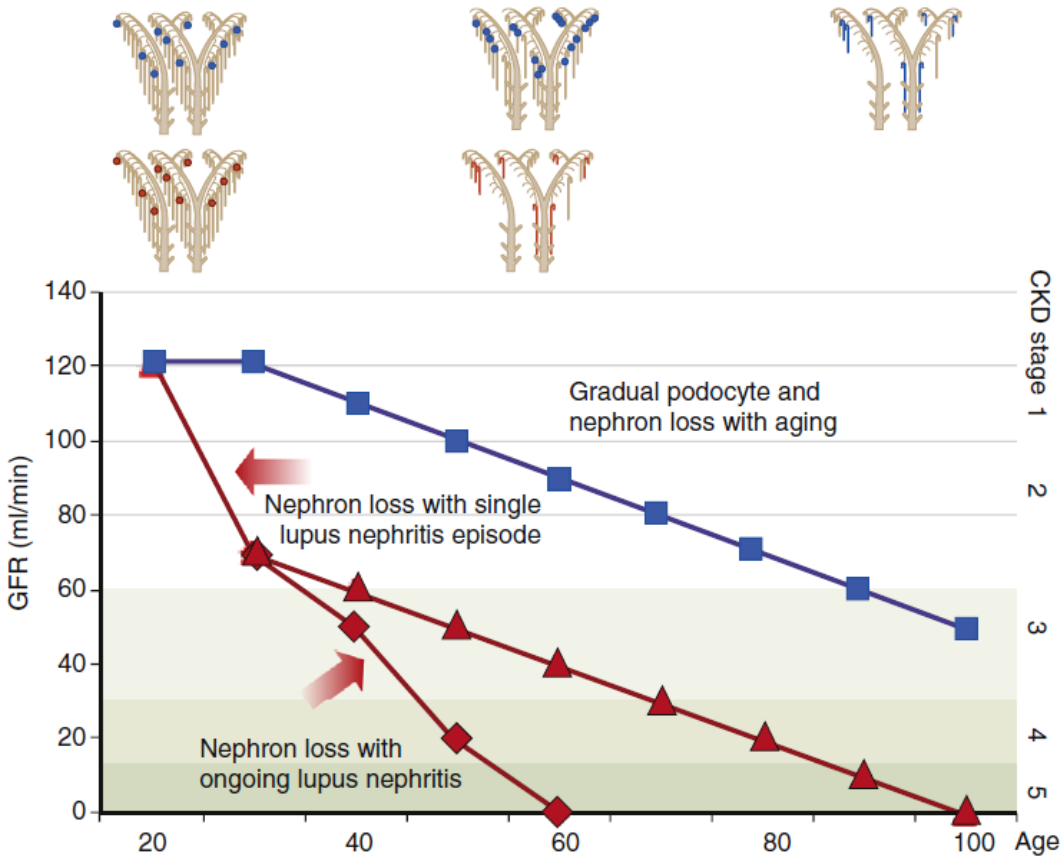

Figure 1. Nephron loss in lupus nephritis; adapted from Rovin et al, 2016. Anders HJ, Rovin B. A pathophysiology-based approach to the diagnosis and treatment of lupus nephritis. Kidney Int. 2016;90(3):493-501.

infection, with a suggested dosing range of 250–1000 mg for 1–3 days. However, some authorities are suggesting no more than a dose of 1–1.5 g of methylprednisolone in total over 3 days,[15] advocating that benefit does not increase while infection risk does. Subsequent oral glucocorticoid doses are recommended at doses of 0.3–0.5 mg/kg/day (Class III/IV) and 20 mg/day (Class V) prednisone equivalent with a rapid taper to ≤5 mg/day.[14]

Additional considerations: Approximately 20% of LN biopsies will show features of thrombotic microangiopathy (TMA), with increased rates observed in the presence of antiphospholipid antibodies. TMA is associated with a worse prognosis. Data on treatment are lacking, although anticoagulation therapy is recommended. TMA should also be considered in the event of a non-response or a plateauing response to initial treatment, or flares, particularly in the absence of changes in standard biomarkers such as dsDNA, complement levels, or proteinuria.[14] **Table 2** on the previous page shows some trends with LN treatment.

Duration of Treatment and Flare Prevention

It is important to keep in mind that there is no cure for SLE. Flares and reactivation may occur at any point in the disease course, and lifelong monitoring for disease activity and flares is necessary. In adults, the continuous age-related loss of podocytes contributes to focal-segmental and later focal-global glomerulosclerosis, leading to an increased risk of chronic kidney disease in the elderly. A single episode of LN can result in significant podocyte and nephron loss, accelerating this risk. Repeated episodes or poor control of LN activity further accelerates nephron loss, increasing the likelihood of ESKD. With the loss of nephrons, the remaining nephrons undergo hypertrophy. As a result, eGFR may overestimate the number of nephrons; thus, a mildly increased serum creatinine may not accurately reflect the extent of nephron loss **(Figure1)**.[16]

These dual concepts emphasize the importance of an adequate duration of treatment and vigilance in preventing flares. Regular

monitoring for LN activity and progression, an appropriate duration of maintenance immunosuppression as above, and continuation of hydroxychloroquine and/or belimumab may all contribute to the prevention of flares. In the event of a flare, a repeat kidney biopsy is commonly indicated to assess for class switching, chronicity, and need for treatment.

Continuation of immunosuppression is recommended for at least three years following renal response. If the initial treatment was with mycophenolate, with or without CNIs or belimumab, these treatments should be continued. If treatment was initially with cyclophosphamide, this should be replaced with mycophenolate or azathioprine. In addition, azathioprine is preferred in patients considering pregnancy or in those who are intolerant to mycophenolate. A gradual withdrawal of immunosuppressive therapy may be considered following at least three years of treatment. Glucocorticoids should be withdrawn first followed by tapering of immunosuppressive drugs.[14] Hydroxychloroquine should be continued indefinitely unless contraindicated. While long-term data on the continuation of belimumab for LN is lacking, data on flare prevention, overall safety profile, and prevention of organ damage support long-term continuation if used initially.

Additional Treatment

Supportive therapies and lifestyle modifications to improve LN outcomes and reduce treatment and disease related comorbidities and adverse events are important. Antihypertensive therapy with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) should be considered in patients with proteinuria and/or hypertension. Statin medications to lower lipid levels may be indicated in some patients. Appropriate immunizations to reduce the risks of infection are imperative. Prevention of osteoporosis with calcium and vitamin D supplementation with or without bisphosphonate therapy should be considered.

Correspondence:

Christine Peschken
Email: Christine.Peschken@umanitoba.ca

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