Appropriate Screening and Management of Lupus Nephritis

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Do	• Do **screen** for lupus nephritis (LN) in patients diagnosed with systemic lupus erythematosus (SLE). This should be performed every **3-6 months** for the first five years after SLE diagnosis and at least **annually** thereafter through urinalysis, serum creatinine, spot urine protein/creatinine ratio (UPCR) or albumin/creatinine ratio (UACR), and immune serology.[1,2,3] • Do involve **multidisciplinary** care for LN, including rheumatology and nephrology.[4] • Do refer to nephrology for consideration of **biopsy** if a patient experiences abnormal or sustained reduction in eGFR, persistent and significantly elevated proteinuria (>500 mg/day), and/or urinalysis with persistent proteinuria/hematuria that cannot be explained by alternate etiology.[1,2,5] • Do prescribe **hydroxychloroquine to all lupus patients** unless contraindicated.[1,4,6,7] • Do maintain a **high index of suspicion for LN**, as undetected or untreated LN may lead to end-stage renal disease (ESRD).[8]
Stop	• Stop use of **non-steroidal anti-inflammatory drugs (NSAIDs)** in patients with chronic kidney disease (CKD), regardless of stage or severity.[9]
Consider	• Consider **treatment modification** following three months of induction therapy if there is less than 25% reduction in proteinuria or no improvement in eGFR.[1, 2] • Consider adjunct therapies to **manage treatment- and disease-related comorbidities**, such as bone health, infection, cholesterol, and blood pressure.[1,2,3] • **Consider initiating induction treatment** for LN in patients with SLE who show compelling clinical and laboratory evidence of rapidly progressing LN (rapid loss of kidney function characterized by consistent decline of eGFR, persistent and significantly elevated proteinuria > 500 mg/day, proteinuria/hematuria on urinalysis, and absence of alternative explanation), but a **biopsy cannot be obtained or is contraindicated**. Lack of biopsy should not substantially delay treatment.[8,10,11]

Background

Lupus nephritis is a common and severe manifestation of SLE, appearing in between 20-60% of patients with lupus over their lifetime. LN is a major risk factor for overall morbidity and mortality in SLE, which can progress to ESRD in ~10% of patients within five years of onset and 22% over 15 years, with the risk being higher in those with diffuse LN.[6,10 12,13,14,15]

Glomerular disease from LN is grouped into six classes. Prognosis is dependent on class, biopsy activity, chronicity of lesions, time to therapy initiation, response to therapy, and patient characteristics.[16]

Six classes of LN (ISN/RPS Classification)
Class I - Minimal Mesangial LN
Class II - Mesangial Proliferative LN
Class III - Focal LN
Class IV - Diffuse LN
Class V - Membranous LN
Class VI - Advanced Sclerosing LN

Screening and Monitoring

Screening and monitoring for LN are important throughout SLE. Early detection and management of LN can result in improved outcomes; therefore, patients should be educated on the symptoms of LN and when to seek help. Symptoms may include general malaise, edema, and hypertension. However, as LN may be asymptomatic, particularly in the early stages, it is critical to actively monitor for LN in patients with SLE.[1,2,4]

LN can be identified through detection of proteinuria and decreasing kidney function, such as increased serum creatinine and decreased eGFR. Any unexplained and persistent decrease in renal function should be promptly investigated. Screening for alternate causes can help to rule out LN, including infections, other intercurrent illnesses, or changes in medications such as NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors.[17]

Methods of screening for LN

Urinalysis is a useful method of screening for LN to detect protein (proteinuria) as well as blood (hematuria) in the urine. Proteinuria is an important biomarker to indicate LN disease activity and measure treatment response. Quantitative methods to determine severity of proteinuria include spot UPCR or UACR. Proteinuria >300 mg/day or sustained decrease in eGFR is a cause for concern, however, retesting is important to confirm persistence or progression. 24-hour urine collection can be used to confirm daily protein excretion and eGFR.[2,18]

Serum immune biomarkers that can be used to monitor SLE and LN disease activity include elevated anti-double-stranded DNA (anti-dsDNA) antibodies and decreased complement components 3 and 4 (C3/C4). Results may assist in the evaluation of disease activity.[2,4,18]

Screening for LN[2]
- Urinalysis to detect proteinuria/hematuria
- Serum creatinine to estimate GFR
- Spot UPCR/UACR to quantify proteinuria
- Immune serology to monitor anti-dsDNA, C3, C4

Timeline:
- Higher risk (e.g., first five years following SLE diagnosis, pediatric patients) = Q 3-6 months
- Lower risk (e.g., ≥5 years following SLE diagnosis and no previous history of LN) = annually

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Biopsy is important for the assessment of LN class, activity, and chronicity features that inform treatment decisions and prognosis.

If a patient experiences abnormal or sustained reduction in eGFR, persistent and significantly elevated proteinuria (>500 mg/day), and/or urinalysis with persistent proteinuria/hematuria that cannot be explained by alternate etiology, a referral to nephrology for consideration of biopsy should be requested. In some patients, management of LN may require repeat biopsy.[2, 6,5,11]

Consider initiating induction treatment for LN if a biopsy can not be obtained or is contraindicated[8]

- In patients with SLE who show compelling clinical and laboratory evidence of rapidly progressing LN, including rapid loss of kidney function characterised by:
  - Consistent **decline** of eGFR.
  - Persistent and significantly elevated **proteinuria > 500 mg/day**.
  - Proteinuria and hematuria on **urinalysis**.
  - Absence of **alternative explanation**.
- Induction treatment should include steroids and immunosuppressants.

Management

Goals for LN treatment include preserving kidney function and avoiding development of morbidity and mortality associated with CKD and kidney failure. Adverse kidney outcomes occur far more frequently in proliferative LN (class III-IV). Current treatment options offer 60-70% probability of partial or complete remission, potentially decreasing eventual progression to ESRD. [1]

Patients with active LN undergoing treatment should be assessed every 1-2 months to evaluate response to therapy, potential adverse events, and treatment adherence.[2] Educating patients on the importance of adhering to their treatment regimen can have a positive impact on outcomes. Medications associated with treatment of LN can have side effects, therefore minimizing drug-associated toxicities is important. Adverse effects include increased susceptibility to infections, malignancies, or bone marrow toxicity.[1,2,15]

- **All patients** with LN should be treated with **hydroxychloroquine** unless contraindicated.[1,4,6,7]
- **Class I/II** treatment may include supportive and/or immunosuppressive treatment and is guided by levels of proteinuria and/or eGFR. Consideration of immunosuppressive treatment is based on SLE symptoms or presence of nephrotic syndrome.[1]
- **Class III/IV** treatment, with or without a membranous component, includes induction therapy to achieve renal response using glucocorticoid and immunosuppressive medications. Once a response is obtained, maintenance therapy is required for a prolonged period to prevent relapse.[1,2,15]
  - **Induction therapy:** [1, 2]
    - Includes either **mycophenolate mofetil** or low-dose intravenous **cyclophosphamide**.
    - Combine with **high-dose glucocorticoids** at 0.35-1.0 mg/kg/day, not to exceed 80 mg/day.[15]
      - Pulse methylprednisone may be considered, however, there exists a paucity of evidence to suggest additional benefit over high-dose oral prednisone.
      - Initiate **tapering** of prednisone at 4-6 weeks or when a reduction is observed in proteinuria (e.g. 25% reduction of proteinuria at 3 months, 50% reduction at 6 months, or stabilization/improvement of eGFR and progressive decline in creatinine).
      - Prednisone use should be tapered to **7.5 mg/day by 3-6 months** following initiation, however, more rapid tapering is recommended, if possible, as prednisone should not be used long term.[4]
    - **Adjuvant treatments** for induction therapy include belimumab or calcineurin inhibitors (CNIs).
      - **Belimumab** may be considered at the start of induction therapy, or within 60 days of induction if eGFR and proteinuria are not improving.[7] Belimumab could also be considered in those with repeated LN flares, with a high risk of progression to ESRD,[15] and/or extra-renal manifestations.
      - **CNIs,** such as tacrolimus or cyclosporin, can be considered in patients with persistent nephrotic range proteinuria and relatively preserved renal function (eGFR > 45 ml/min/1.73 m2) or for those who cannot tolerate other immunotherapies.[1,2,15]
  - **Assess treatment response:**[1,2,5]
    - A change in treatment should be considered if, after **three months** of treatment, there is inadequate renal response, considered less than 25% reduction in proteinuria, or no improvement in eGFR. Ensure adequate dosing and medication adherence, as well as confirming no alternate pathologies, prior to switching.
    - Options include higher-dose glucocorticoid, combined with switching induction medication to the alternate therapy (i.e. cyclophosphamide <-> mycophenolate); with the possible addition of belimumab, rituximab, or CNIs.[7]
  - **Maintenance therapy:**[1, 2]
    - Continuation of mycophenolate (usually at lower dose than used during induction) as well as maintenance of any adjuvant therapies can be considered following **adequate renal response**. Azathioprine is the preferred maintenance medication in those contemplating pregnancy and in those unable to tolerate mycophenolate.
    - **Phased withdrawal of maintenance therapy** (glucocorticoids first, then immunosuppressive drugs) may be considered following at least three years of treatment, including one year of complete clinical remission after stopping prednisone. Hydroxychloroquine should be continued long term. The presence of persistently low complements (C3 or C4) or persistently elevated anti-dsDNA are

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associated with higher risk of flare. Withdrawal of immunosuppressive therapy should be carefully considered in patients with CKD to avoid potential further decline in kidney function.

- **Class V** – Data on recommended management for class V LN is limited. Monitoring of proteinuria levels and prevention/treatment of complications is recommended. There is a strong consensus for the use of prednisone for patients in the nephrotic range, with consideration for additional immunomodulatory agents determined by local nephrology guidance and patient factors (e.g. non-renal symptoms, increasing proteinuria, or complications of proteinuria such as edema or thrombosis). [1, 5]
- **Class VI** treatment includes renal replacement therapy. [1, 5]

Addressing additional risk factors

Adjunctive therapies and lifestyle modifications to manage LN and attenuate treatment- and disease-related comorbidities should be considered:[1,7,19]

- Statin medication to lower lipids, as SLE, LN, and CKD increase cardiovascular morbidity and mortality.
- Antihypertensive therapy with either ACE inhibitors or ARBs in patients with proteinuria and/or hypertension.
- Calcium and vitamin D supplementation, as well as consideration of anti-resorptive agents (based on eGFR), to protect against bone injury.
- Consideration of appropriate immunizations with non-live vaccines to reduce risk of infection.

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