

Update on Lupus Nephritis: Core Curriculum 2020

Samir V. Parikh, Salem Almaani, Sergey Brodsky, and Brad H. Rovin



Systemic lupus erythematosus is a multisystem autoimmune disease that commonly affects the kidneys. Lupus nephritis (LN) is the most common cause of kidney injury in systemic lupus erythematosus and a major risk factor for morbidity and mortality. The pathophysiology of LN is heterogeneous. Genetic and environmental factors likely contribute to this heterogeneity. Despite improved understanding of the pathogenesis of LN, treatment advances have been few and risk for kidney failure remains unacceptably high. This installment in the Core Curriculum of Nephrology provides an up-to-date review of the current understanding of LN epidemiology, pathogenesis, diagnosis, and treatment. Challenging issues such as the management of LN in pregnancy, timing of transplantation, and the evolving role of corticosteroid use in the management of LN are discussed. We review the currently accepted approach to care for patients with LN and highlight deficiencies that need to be addressed to better preserve long-term kidney health and improve outcomes in LN.

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Epidemiology

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that predominantly affects women of child-bearing age and often involves the kidneys. Lupus nephritis (LN) occurs in ~50% of patients with SLE and is the most common, but not the only, cause of kidney injury in SLE. Men with SLE tend to have more aggressive disease with higher rates of renal and cardiovascular involvement and are more likely to develop kidney failure than women.

Patients with SLE who develop LN present at a younger age than patients with SLE without nephritis. Additionally, LN typically develops early in the disease course, generally within the first 6 to 36 months, and may be present at initial diagnosis. Risk factors for the development of LN include younger age, male sex, and non-European ancestry. In the United States, the incidence of LN is higher in black (34%-51%), Hispanic (31%-43%), and Asian (33%-55%) compared with white (14%-23%) patients. Black and Hispanic patients have worse outcomes and are more likely to progress to kidney failure than white patients. Black and Hispanic patients tend to have more severe underlying histopathology, higher serum creatinine levels, and more proteinuria than white patients at LN diagnosis. Additionally, autoantibodies strongly associated with LN, including anti-Sm, anti-Ro, and anti-ribonucleoprotein antibodies, are more frequently positive in black compared with white patients. The reasons for these racial and ethnic differences are not completely understood, but genetic and socioeconomic factors likely contribute.

Mortality associated with lupus is significantly higher in those with LN compared with those without LN, and death directly attributable to kidney disease occurs in 5% to 25% of patients with proliferative LN within 5 years of onset. Furthermore, 10% to 30% of patients with LN progress to kidney failure requiring kidney replacement therapy (KRT). Patients with proliferative forms of LN (class III, IV, or III/IV + V) are at highest risk for requiring KRT. Achieving a complete clinical response to treatment is critical to preserving long-term kidney health. In one study, patients who achieved a complete clinical response had 92% kidney survival at 10 years compared to 43% in partial responders and 13% in nonresponders. Overall, the kidney failure risk associated with LN improved from the 1970s to 2000. However, since 2000, the rate of LN requiring KRT has remained consistent and there is evidence to suggest that these rates are increasing now, particularly in black populations.

Additional Readings

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

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Genetics and Pathophysiology of LN

Genetics of LN

SLE occurs in genetically predisposed individuals who are exposed to environmental triggers. Several risk alleles associated with SLE have also been implicated in LN, but genetic studies specifically evaluating LN are lacking. Genome-wide association studies have identified risk genes in LN that are not otherwise seen in patients with SLE without nephritis, including apolipoprotein L1 (APOL1), platelet-derived growth factor receptor alpha (PDGFRA), and hyaluronan synthase 2 (HAS2). Genetic modifications in HLA alleles are also associated with LN. HLA-DR4 and HLA-DR11 appear to protect against LN, while HLA-DR3 and HLA-DR15 confer increased risk. A recent genome-wide association study identified more than 50 genetic polymorphisms associated with multiple physiologic processes known to be aberrant in LN.

Genetic variations likely contribute to the racial and ethnic disparities of lupus and LN. For example, allelic variants in Fc receptor IIA for immunoglobulin G (IgG; Fcγ RIIA) are more common in black patients with SLE and specifically in LN compared with controls without SLE, possibly contributing to a reduced capacity for immune complex clearance in black patients. Allelic variants in the APOL1 gene are associated with increased risk for kidney failure in black populations and in LN; those with 2 risk alleles for APOL1 have more than 2.5-fold increased risk for developing kidney failure compared with those without risk alleles.

The presence of risk alleles alone is not enough to explain the development of SLE or LN, and not all patients with SLE have variants that increase risk. Larger studies involving racially and ethnically diverse cohorts are needed to better appreciate the contribution of genetics to LN.

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Pathophysiology of LN

Abnormalities in innate and adaptive immunity contribute to the pathogenesis of lupus. Characteristically,

autoantibodies directed against nuclear and cellular antigens are produced, leading to immune complex formation and accumulation of immune complexes in glomeruli. Immune complexes may deposit in glomeruli from the circulation or may form in situ if autoantibodies target intrinsic glomerular antigens (such as annexin 2) or antigens that are released during apoptosis and/or arise when apoptotic debris (including chromatin) is incompletely cleared. Chromatin can also activate intrarenal dendritic cells, increase the interaction of T and B cells, and enhance the production of anti-chromatin antibodies. Intraglomerular immune complexes can activate complement and engage leukocyte Fc receptors to initiate intrarenal inflammation and injury. Complement-mediated kidney damage, especially through the alternative pathway, has been observed in murine and human LN.

Interstitial plasma cells generated from T- and B-cell aggregates within the kidney tubulointerstitium may also produce clonally restricted autoantibodies. This kidney-specific autoimmunity is facilitated by intrarenal interferon α (IFN- α) expression. Immune complexes are ligands for Toll-like receptors (TLRs), specifically TLR7 and TLR9. TLR7/9 engagement induces IFN- α expression by plasmacytoid dendritic cells, which enhances production of antigen-presenting cells, encourages autoreactive B-cell differentiation to plasma cells, and enhances production of CD4 helper T (T_H) and CD8 memory T cells, leading to further autoantibody generation and immune complex formation.

Abnormalities in B-cell tolerance leading to autoantibody production is seen in lupus. Human regulatory T cells normally suppress B- and T-cell-mediated autoantibody production but are reduced in number and functionally defective in SLE. Autoreactive B cells process and present self-antigens to T cells, promoting proinflammatory cytokine activation. T_H1 cytokines are particularly overexpressed in LN kidneys and promote inflammation through macrophage, complement, and Fc receptor activation. In addition, T_H1 cells promote differentiation and proliferation of B cells and assist class switching of autoantibodies to isotypes that are more specific for renal antigens. For example, IgG1 and IgG3 autoantibodies have been associated with LN and promote intrarenal inflammation through complement-mediated leukocyte recruitment.

Immune complex clearance by leukocytes is impaired by the presence of low-affinity Fcγ receptors and autoantibodies to C1q and C3b. Engagement of low-affinity Fcγ receptors by immune complexes promotes leukocyte activation. Activated neutrophils and macrophages directly injure the kidney through secretion of oxygen free radicals and proteolytic enzymes. Dying neutrophils release neutrophil extracellular traps. These chromatin structures bind autoantigens and further stimulate IFN- α secretion from dendritic cells, amplifying intrarenal autoimmunity.

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Diagnosis and Clinical Presentation

Case 1: A 32-year-old woman with a history of SLE associated with malar rash and polyarthritis is referred to you for evaluation of proteinuria discovered by routine urinalysis.

Question 1: Which of the following is correct regarding the diagnostic workup of LN?

- a) Proliferative LN does not occur with urine protein excretion < 1,000 mg/d
- b) An absence of dysmorphic red blood cells (RBCs; acanthocytes) on urine microscopy rules out LN
- c) Spot urinary protein-creatinine ratios (UPCRs) are unreliable for accurate assessment of proteinuria in patients with LN
- d) Urine concentration (specific gravity) does not influence interpretation of proteinuria with urine dipstick

For the answer to the question, see the following text.

The clinical identification of LN can be challenging because patients often lack overt signs of kidney disease, especially early. Instead, LN is most commonly discovered after careful examination of urine and laboratory data in patients with lupus. Assessment of serum creatinine level, urine dipstick testing, and urine sediment examination are necessary screening tools for LN evaluation. Many patients will have findings suggestive of LN at the initial diagnosis of SLE, and patients with SLE should undergo screening for

LN at diagnosis, at least yearly thereafter, and any time there is concern for a lupus flare.

A positive test result for blood and/or protein on urine dipstick in a patient with lupus is suggestive of nephritis, but should be interpreted with caution. The urine dipstick may be falsely negative for proteinuria when the urine concentration is dilute (ie, low specific gravity) or falsely positive for significant proteinuria when urine is highly concentrated (ie, high specific gravity). Additionally, the urine dipstick is highly sensitive for blood and may be falsely positive or represent bleeding from a nonglomerular source, such as menstruation in a young woman. Therefore, urine microscopy should always accompany the dipstick. Findings specific for glomerular bleeding associated with nephritis include dysmorphic RBCs, specifically acanthocytes (Fig 1A) and RBC casts (Fig 1B). Microscopic hematuria is present in ~80% of patients with LN, while RBC casts are present in 30%. White blood cells and white blood cell casts (Fig 1C) in the absence of infection may also be present and are consistent with intrarenal inflammation that can be present in LN.

By definition, proteinuria must be present to clinically diagnose LN. Nephrotic-range proteinuria (protein excretion > 3.5 g/d) is found in up to 50% of cases. Quantification of proteinuria can be performed either by measuring UPCR in a random spot specimen or a 24-hour urine collection. UPCR from a spot sample, though convenient, can be inaccurate in LN, over- or underestimating the true level of proteinuria. Thus, although a spot urine specimen can be used to screen and follow trends in individual patients, for critical clinical decisions such as changing treatment, it should be verified by a 24-hour urine collection. Measurement of UPCR in 24-hour urine attenuates collection errors. Even an intended 24-hour collection that is at least 50% complete correlates well with a complete 24-hour collection. A first-morning-void UPCR also accurately reflects 24-hour proteinuria in LN.

The gold standard for diagnosis and classification of LN is the percutaneous kidney biopsy. Though the proteinuria threshold for which a biopsy should be considered is not well defined, evidence from observational studies suggests that urine protein excretion greater than 500 to 1,000 mg/d is associated with significant kidney inflammation, especially during the first episode of LN when the kidney may not have a lot of long-term damage that could result in proteinuria without inflammation. Because early disease recognition and treatment is important to long-term preservation of kidney health, we recommend a kidney biopsy when urine protein excretion exceeds 500 mg/d. Biopsy should be done at any level of proteinuria with decreased glomerular filtration rate (GFR) that is not readily attributed to another cause, for example, a new medication. Alternatively, a biopsy may not be required if the only clinical abnormalities indicative of LN are asymptomatic microscopic hematuria or proteinuria with protein excretion < 500 mg/d in the absence of active urine sediment. A general approach to the diagnosis and management of LN is shown in Figure 2.

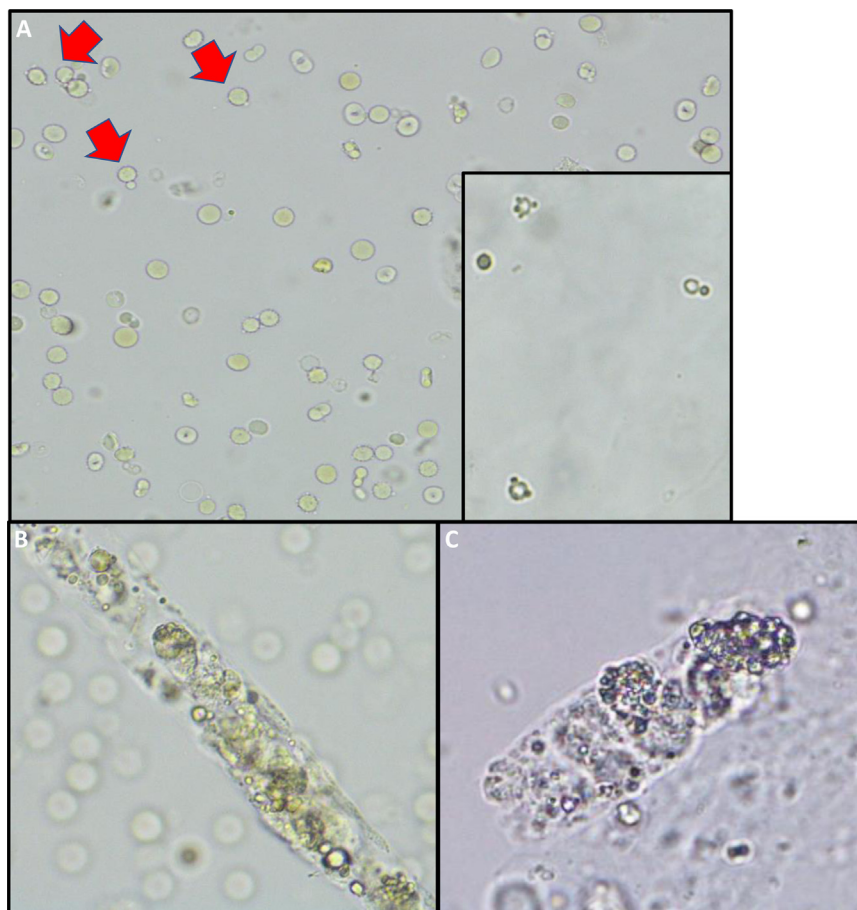


Figure 1. Urine microscopy in lupus nephritis. (A) Dysmorphic red blood cells with acanthocytes, characteristic of glomerular bleeding, noted by red arrows. The bottom right corner is an enhanced image showing acanthocytes. (B) A red blood cell cast. (C) A white blood cell cast.

Returning to question 1, the correct answer is (c). There is ample evidence that the correlation of UPCR from spot and 24-hour specimens is modest at best, and the former should not be used for initial workup of a patient with suspected LN. Regarding (a), proliferative LN may occur at even low levels of proteinuria. Answer (b) is incorrect because although acanthocytes are specific for glomerular bleeding, their absence does not rule out nephritis. Answer (d) is wrong because on urine dipstick, a concentrated or dilute urine specimen can lead to a falsely high- or low-level proteinuria read out, respectively.

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The Role of the Kidney Biopsy

Case 2: An 18-year-old woman with a history of SLE has class IV LN diagnosed. She is treated with mycophenolate mofetil (MMF) and prednisone. After 2 months of stable laboratory readings on treatment, her kidney function starts to worsen and she develops new-onset hypertension. Over 2 weeks, her serum creatinine level increases from 0.9 to 3.5 mg/dL. Blood pressure is now 160/90 mm Hg. She has been adherent to treatment.

Question 2: Which of the following are appropriate next steps?

- a) Given the patient has proved unresponsive to MMF, she should be switched to intravenous (IV) cyclophosphamide
- b) Check antiphospholipid antibody (APLA) titers
- c) Increase prednisone to 60 mg daily
- d) Start rituximab treatment

For the answer to the question, see the following text.

At present, kidney biopsy is used to establish a diagnosis of LN or other processes involving the kidneys in a patient with lupus; to correctly classify LN, which may have

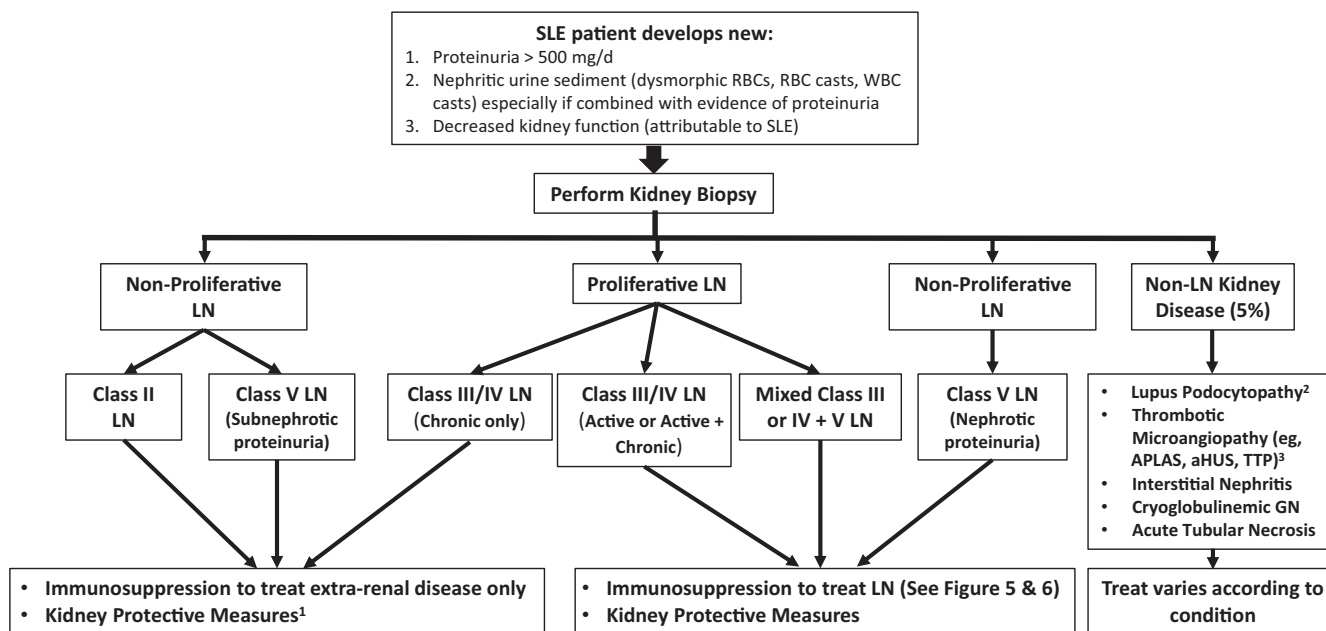


Figure 2. Diagnostic approach to kidney disease associated with systemic lupus erythematosus (SLE). An algorithmic approach to diagnosis and general treatment strategies according to biopsy findings is shown. Patients with SLE with clinical evidence of kidney injury undergo kidney biopsy and based on biopsy findings, the appropriate treatment strategy is applied. ¹Kidney protective measures: used for all patients with any form of lupus nephritis (LN). Includes antiproteinuric therapy with blockade of renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, strict blood pressure control (<125/75 mm Hg), moderate sodium- and protein-restricted diet, and correction of metabolic abnormalities. ²Lupus podocytopathy: focal segmental glomerulosclerosis or minimal change disease associated with SLE and causes nephrotic syndrome. Treatment with high-dose steroids is usually effective. Additional immunosuppression as needed to control extrarenal disease. ³Thrombotic microangiopathy: may be acute, subacute, or chronic changes seen in biopsy. May be due to antiphospholipid antibody syndrome (APLAS), atypical hemolytic uremic syndrome (aHUS), or thrombotic thrombocytopenic purpura (TTP). Treatment is directed at underlying cause. Abbreviations: GN, glomerulonephritis; RBC, red blood cell; WBC, white blood cell.

therapeutic and prognostic implications; and to determine the extent of acute and chronic kidney injury, which has therapeutic implications. Besides LN, kidney injury in patients with lupus could be due to thrombotic microangiopathy (TMA)/antiphospholipid nephropathy, non-immune complex podocytopathy, tubulointerstitial nephritis, acute tubular necrosis, renovascular disease, or nephrotoxicity from medications (Fig 2). TMA may be present in up to 25% of cases of kidney injury associated with SLE. Importantly, treatment of TMA is different from LN and early recognition of TMA is critical to preserving GFR because the ischemia that results from TMA can rapidly lead to accumulation of chronic kidney damage.

Lupus podocytopathy is seen in 1% to 2% of patients with SLE and presents with nephrotic syndrome. Clinically it is difficult to distinguish lupus podocytopathy from LN, especially class V LN. However, histologically, lupus podocytopathy is more readily distinguished from LN. Light microscopy reveals normal-appearing glomeruli or glomeruli with a focal segmental glomerulosclerosis pattern with or without mesangial proliferation. Electron microscopy demonstrates diffuse foot-process effacement

and an absence of subendothelial or subepithelial deposits. Additionally, lupus podocytopathy is more amenable to treatment and often rapidly responds to corticosteroid therapy alone.

Although the role of a kidney biopsy at first presentation of kidney involvement in lupus is well established, the role for a repeat kidney biopsy is less clear. Generally, repeat kidney biopsies have been done on a “for cause” basis, for example, a flare of LN, treatment-resistant disease, or in cases in which it is unclear whether persistent proteinuria is due to active disease or chronic nephrosclerosis (Fig 3).

Protocol repeat biopsies are more controversial, but emerging data from observational cohort studies suggest that such biopsies may assist in making treatment decisions and help predict long-term renal outcomes. Protocol repeat biopsies have shown considerable discrepancies between clinical and histologic findings. For example, repeat biopsies done after 6 to 8 months of treatment in patients with a complete clinical response showed significant persistent histologic activity in 20% to 50% of cases. Additionally, 40% to 60% of patients had persistent proteinuria with protein excretion > 500 mg/d and were

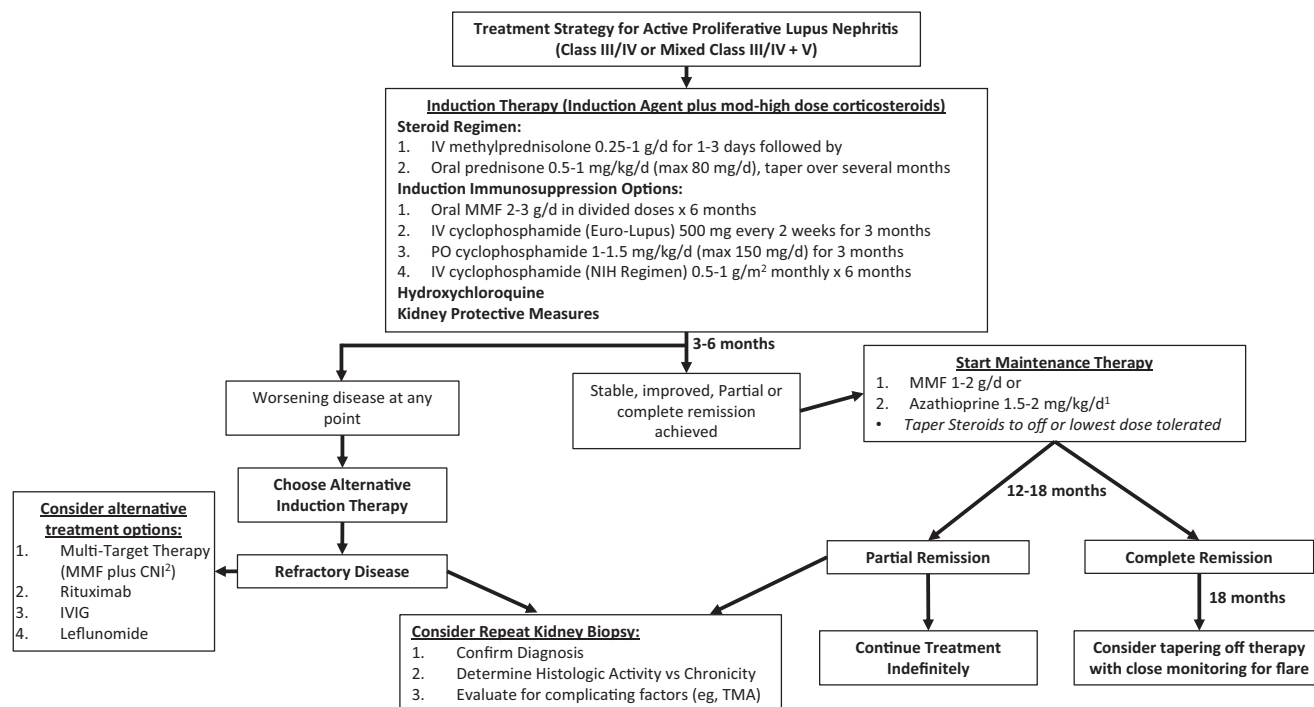


Figure 3. Treatment of proliferative lupus nephritis (LN). An approach to management of proliferative LN is shown. After a diagnosis of class III/IV or III/IV+V LN is made, immunosuppressive therapy is started with intravenous (IV) methylprednisolone followed by a high-dose corticosteroid taper and either mycophenolate mofetil (MMF) or cyclophosphamide for induction therapy. Induction therapy continues for 3 to 6 months and is followed by maintenance therapy with either MMF or azathioprine. After 12 to 18 months of treatment, if complete response is achieved, consider slow taper of maintenance therapy. If partial response is achieved, continue treatment indefinitely but consider repeat biopsy to determine whether active lesions are still present. If no response to initial treatment, switch to the alternative induction agent; if receiving MMF, switch to cyclophosphamide or vice versa. If the kidney function worsens despite induction therapy, consider repeat biopsy to confirm diagnosis and ensure that a secondary process such as thrombotic microangiopathy (TMA) is not present. ¹Before initiating azathioprine, we recommend checking thiopurine methyltransferase (TPMT) activity. Azathioprine use should be avoided in the setting of TPMT deficiency because it can lead to potentially life-threatening bone marrow toxicity at usual doses. ²CNI, calcineurin inhibitor therapy; includes tacrolimus and cyclosporine.

not considered to have achieved complete remission but showed no histologic activity on repeat biopsy. Recently, a prospective randomized controlled trial (RCT) studied the role of a protocol repeat biopsy in patients who had been in complete renal remission for 1 year and had received at least 36 months of immunosuppressive treatment. Therapy was withdrawn in all these patients and they were followed up prospectively for 24 months to assess for LN flare. Overall, 11 of 36 patients experienced a flare, 10 of whom had a histologic activity index > 2 on the repeat biopsy despite being in clinical remission. These observations suggest that a repeat biopsy done when considering withdrawal of maintenance immunosuppression may help guide that decision.

For question 2, the correct answer is (b). Rapid decline in kidney function accompanied by new-onset hypertension in a patient who has been otherwise stable and adherent to medications should raise the possibility of antiphospholipid antibody syndrome. The workup of

antiphospholipid antibody syndrome includes checking APLA titers and assessing for venous and arterial thromboembolism and TMA. Although LN can definitely relapse, a very severe relapse after 2 months of stable disease without extrarenal symptoms is less likely. Therefore, the other answers are incorrect. Additionally, the clinical presentation is concerning for a TMA.

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Treatment Response Criteria in LN

Case 3: A 24-year-old woman with a history of LN treated with low-dose cyclophosphamide followed by maintenance with MMF presents for her 1-year follow-up. Creatinine level is 0.9 mg/dL and proteinuria of 0.6 g/d. She has RBCs (1+) on urine dipstick. She is worried about her long-term kidney health and asks about her renal prognosis.

Question 3: Based on the current evidence, which one of the following statements is correct about her long-term kidney health?

- She has a favorable long-term kidney prognosis based on 12-month proteinuria level
- She has a poor long-term kidney prognosis due to persistent hematuria at 12 months
- The combination of 12-month hematuria and proteinuria is more predictive of long-term kidney health than proteinuria level alone

For the answer to the question, see the following text.

Treatment response in LN is defined clinically and generally stratified into complete (CR), partial (PR), and no response. Guideline definitions for clinical response in LN have been suggested by several organizations (Table 1). Although there is no consensus definition of CR across guidelines, proteinuria is the most important clinical variable used to define response. In general, a reduction in protein excretion to <0.5 g/d based on a 24-hour urine collection with normal serum creatinine or serum creatinine level within 15% of previous baseline is considered a CR. Urine sediment findings are also important for individual patients but have not been found useful in multicenter clinical trials due to issues of reproducibility. PR

requires $> 50\%$ reduction in proteinuria and to non-nephrotic levels, with serum creatinine level within 25% of previous baseline. Patient who do not achieve CR or PR are considered nonresponders. Nonresponders include patients who show some response but do not meet PR criteria, have no improvement in parameters, or are worse.

In the clinical trial setting, responses are typically evaluated at 6 to 12 months. Whether short-term responses predict long-term outcomes in LN has been questioned. To address this question, a retrospective analysis of 1-year clinical response metrics from the Euro Lupus Nephritis Trial (ELNT) were correlated with kidney outcomes after at least 7 years of follow-up. Proteinuria with protein excretion < 800 mg/d at 1 year was the best predictor of good long-term renal outcome. The addition of serum creatinine level and microscopic hematuria did not improve the prediction model. These findings were confirmed in independent cohorts. Although these data suggest that the current definition of LN response may need to be modified to create a uniform definition according to proteinuria level at 1 year, the patients studied were predominantly white. Confirmation from prospective clinical trials in multiethnic populations is required before a relaxed proteinuria definition for clinical response can be formally accepted into clinical practice.

With respect to question 3, the correct answer is (a). Data from ELNT demonstrated that proteinuria with protein excretion < 0.8 g/d at 1 year is the best predictor of long-term prognosis. In the same cohort, the absence of hematuria had a good positive predictive value for a favorable long-term prognosis. However, the presence of hematuria did not have a strong negative predictive value. The combination of proteinuria and hematuria decreased the performance of the predictive model.

Table 1. Clinical Response Criteria According to Current Guidelines

Guideline	Complete Response Criteria	Partial Response Criteria	No Response
KDIGO	Decline in UPCR to ≤ 0.5 g/g (≤ 50 mg/mmol); return of Scr to previous baseline	$>50\%$ decrease in UPCR; if there was nephrotic-range proteinuria, then reduction to $<3,000$ mg/g [<300 mg/mmol] also; stabilization ($\pm 25\%$), or improvement of Scr, but not to normal	Failure to achieve a complete or partial remission
ACR	UPCR < 0.2 g/g; normal Scr, or 25% improvement in eGFR if abnormal at LN flare; inactive urine sediment	UPCR of 0.2-2 g/g; eGFR at baseline level or improves 25% if abnormal at LN flare; inactive urine sediment	No change or worsening proteinuria; decline in eGFR by $\geq 25\%$; active urine sediment
EULAR/ERA-EDTA	UPCR < 0.5 g/g (<50 mg/mmol); GFR within 10% of previous normal	$\geq 50\%$ reduction in UPCR, to less than nephrotic range; near-normal GFR (within 10% of prior baseline) by 12 mo of treatment	$<50\%$ reduction in proteinuria or persistent nephrotic proteinuria; abnormal GFR ($>10\%$ decrease from prior baseline)
Dutch SLE Working Group	Proteinuria < 0.5 g/24 h; Scr within 25% of baseline before flare	Reduction in proteinuria by $>50\%$ to <3 g/24 h; Scr within 25% of prior baseline by 6-12 mo of treatment	Persistent proteinuria with $<50\%$ reduction or persistently >3 g/24 h after 6-12 mo; doubling of Scr within 3 mo of starting therapy

Abbreviations: ACR, American College of Rheumatology; eGFR, estimated glomerular filtration rate; EULAR/ERA-EDTA, European League Against Rheumatism/European Renal Association–European Dialysis and Transplant Association; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; LN, lupus nephritis; Scr, serum creatinine; SLE, Systemic lupus erythematosus; UPCR, urinary protein-creatinine ratio.

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Histopathologic Classification of LN

The currently accepted histopathologic classification of LN is the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) system, but updates to simplify the categories and assess the tubulointerstitium more carefully have been proposed. The ISN/RPS classification does not account for this compartment and although National Institutes of Health (NIH) injury indexes attempted to account for both glomerular and tubulointerstitial lesions, their reproducibility and prognostic utility has been questioned. To address these limitations, a working group of expert Nephropathologists released consensus recommendations to update the ISN/RPS classification and NIH activity indexes. A description of the ISN/RPS classification and the proposed changes are shown in [Table 2](#).

Briefly, the ISN/RPS classification is based solely on the location of immune complex deposits within glomeruli, the extent of glomerular involvement, and whether the injury pattern reflects acute inflammation (active disease) or sclerosis (chronic disease). LN is differentiated into 6 classes and glomerular lesions are characterized as either active (A) or chronic (C) and segmental (<50% glomerular capillary tuft involvement) or global (≥50% glomerular capillary tuft involvement). [Figure 4](#) shows the characteristic glomerular lesions seen in LN by light and electron microscopy. [Figure 5](#) shows the characteristic “full house” pattern on immunofluorescence classically seen in LN, but not required for diagnosis. This immunofluorescence pattern refers to the presence of all immunoreactants including IgG, IgA, IgM, C1q, and C3. Additionally, C1q is fairly specific for LN. IgG subclass staining usually demonstrates dominant IgG1 and IgG3, mild IgG2, and minimal IgG4.

Additional Readings

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Treatment of LN

Case 4: A 35-year-old man with recently diagnosed SLE presents with urine protein excretion of 4 g/d, elevated serum creatinine level at 1.3 mg/dL, and microscopic hematuria. Anti-double-stranded DNA antibody levels are elevated and C3 level is low. He undergoes kidney biopsy, which is consistent with class IV+V LN.

Question 4: Which of the following should be included as part of your discussion with the patient regarding treatment of his LN?

- a) MMF is superior to cyclophosphamide for treatment of LN
- b) Immunosuppressive treatment is typically required for at least 24 months and often longer
- c) Hydroxychloroquine use is not indicated in LN because it has not been shown to be associated with improved LN treatment response
- d) Large RCTs have demonstrated that rituximab when added to standard of care (SOC) is superior to SOC alone for inducing remission in LN

For the answer to the question, see the following text.

General Principles in LN Management

The management of LN varies according to disease severity and risk for progressive kidney damage. Nonproliferative forms of LN include class II and V LN with sub-nephrotic-range proteinuria and normal GFR and are generally treated conservatively with treatment focused on blood pressure control with renin-angiotensin system blockade and immunomodulation with antimalarials (eg, hydroxychloroquine). Immunosuppression is used as needed to treat extrarenal manifestations only. In addition to antimalarials and renin-angiotensin system blockade, proliferative forms of LN (class III, IV, or III/IV+V) and class V LN with nephrotic syndrome are treated with systemic immunosuppression combined with high-dose corticosteroids to suppress inflammation and control autoimmunity. This initial phase of treatment is called the induction phase and typically lasts 3 to 6 months.

It is followed by a prolonged maintenance phase of treatment in which immunosuppressive and anti-inflammatory therapy is continued but de-escalated slowly over time to limit risk for LN flare. The maintenance phase of treatment may

Table 2. 2003 ISN/RPS LN Histopathologic Classification, NIH Injury Indexes and Proposed Changes

Classification	Category	Description	Proposed Modification
ISN/RPS	Class I	Normal glomeruli by LM, mesangial immune complexes on IF or EM	No changes recommended
ISN/RPS	Class II	Pure mesangial hypercellularity with mesangial immune deposits; mesangial matrix expansion seen by LM	Definition for mesangial hypercellularity is provided; ≥ 4 nuclei surrounded by matrix in the mesangial area
ISN/RPS	Class III	Focal segmental or global disease involving $<50\%$ of all glomeruli III (A): active lesions III (A/C): active and chronic lesions III (C): chronic inactive lesions	1. Endocapillary proliferation is replaced by endocapillary hypercellularity 2. Crescent $>10\%$ of Bowman capsule circumference (cellular crescent, $>75\%$ cells, $<25\%$ fibrous matrix; fibrocellular crescent, $25\%-75\%$ cells and fibrin, remainder is fibrous matrix; fibrous crescent $>75\%$ fibrous matrix, $<25\%$ cells)
ISN/RPS	Class IV	Diffuse segmental (S) or global (G) disease involving $\geq 50\%$ of all glomeruli IV-S: $\geq 50\%$ glomeruli with segmental lesions IV-G: $\geq 50\%$ glomeruli with global lesions IV-S(A), IV-G(A): active lesions IV-S(A/C), IV-G(A/C): active and chronic lesions IV-S(C), IV-G(C): chronic inactive lesions	3. Adhesion defined as an area of isolated continuity of ECM material between tuft and capsule; fibrinoid necrosis is fibrin associated with basement membrane disruption and/or lysis of mesangial matrix 4. Eliminate global and segmental designations from class IV LN 5. Indicate whether tubulointerstitial lesions occur in presence or absence of interstitial fibrosis
ISN/RPS	Class V	Global or segmental subepithelial immune deposits with GBM thickening; mesangial immune complex deposits may be present; may occur in combination of class III or IV	No changes recommended
ISN/RPS	Class VI	Advanced sclerosis; $\geq 90\%$ of glomeruli are sclerosed	No changes recommended
NIH activity indexes	a) Glomerular endocapillary hypercellularity b) Glomerular leukocyte infiltration c) Glomerular fibrinoid necrosis, karyorrhexis d) Glomerular subendothelial deposits-wire loop lesions e) Glomerular cellular crescents f) Interstitial inflammation	Active lesions scoring: 0-24 Each lesion scored 0-3: 1+: $<25\%$ of glomeruli 2+: $25\%-50\%$ of glomeruli 3+: $>50\%$ of glomeruli involved For interstitial lesions: 1+: $<25\%$ interstitial leukocytes 2+: $25\%-50\%$ interstitial leukocytes 3+: $>50\%$ interstitial leukocytes Fibrinoid necrosis and crescents are double the weight (0-3 \times 2)	Modified NIH injury indexes reported with each biopsy and replaces active and chronic designations for proliferative (class III/IV lesions) Active Lesion Proposed Changes: 1. Separate fibrinoid necrosis from karyorrhexis 2. Fibrocellular recognized with cellular crescent as active lesion 3. Leukocyte infiltration is removed
NIH chronicity indexes	a) Glomerular sclerosis b) Glomerular fibrous crescents c) Tubular atrophy d) Interstitial fibrosis	Chronic lesions scoring: 0-12 Each lesion scored 0-3: 1+: $<25\%$ of glomeruli 2+: $25\%-50\%$ of glomeruli 3+: $>50\%$ of glomeruli For tubulointerstitial lesions: 1+: $<25\%$ tubular atrophy and/or interstitial fibrosis 2+: $25\%-50\%$ tubular atrophy and/or interstitial fibrosis 3+: $>50\%$ tubular atrophy and/or interstitial fibrosis	Modified NIH injury indexes reported with each biopsy and replaces active and chronic designations for proliferative (class III/IV lesions) Chronic lesions: create a total glomerular sclerosis score (global + segmental)

Abbreviations: ECM, extracellular matrix; EM, electron microscopy; GBM, glomerular basement membrane; IF, immunofluorescence; ISN/RPS, International Society of Neurology/Renal Pathology Society; LM, light microscopy; LN, lupus nephritis; NIH, National Institutes of Health.

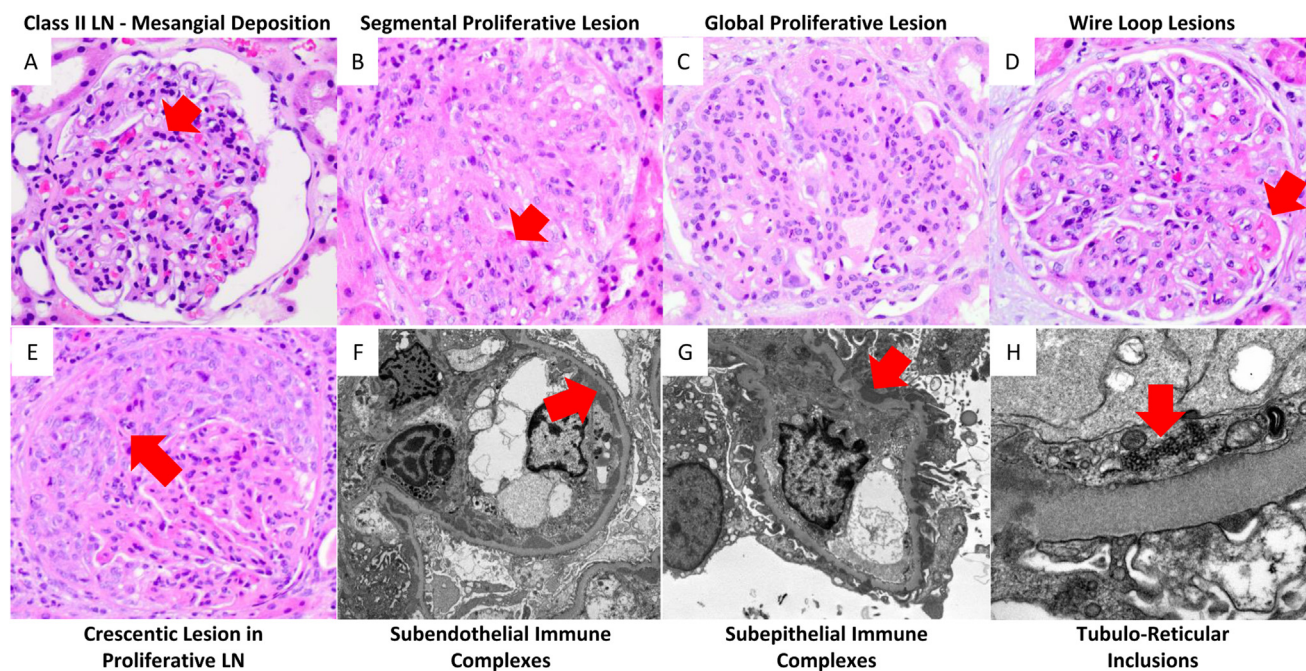


Figure 4. Histologic lesions of lupus nephritis (LN). (A-E) Light microscopic images demonstrate typical glomerular lesions found in LN. (A) Mesangial hypercellularity seen in class II LN. (B-E) Inflammatory lesions seen in proliferative forms of LN. (F-H) Characteristic electron microscopic findings of LN. (F) Subendothelial deposits are seen in proliferative forms of LN, while (G) subepithelial deposits are seen in membranous LN. (H) Tubuloreticular inclusions that are commonly found in LN biopsy specimens and are thought to reflect increased interferon expression.

last several years, though the exact duration is unclear and currently is considered on a patient-to-patient basis.

The Role of Antimalarials in LN

Antimalarials are immunomodulators that act on the innate immune system by blocking TLR signaling on plasmacytoid

dendritic cells, reducing production of IFN- α and downstream proinflammatory cytokines. Antimalarials are also anti-inflammatory and anti-thrombotic and are safe to use in pregnancy. In LN, antimalarial treatment has been shown to improve 12-month renal response rates, reduce flare risk, and delay progression to kidney failure.

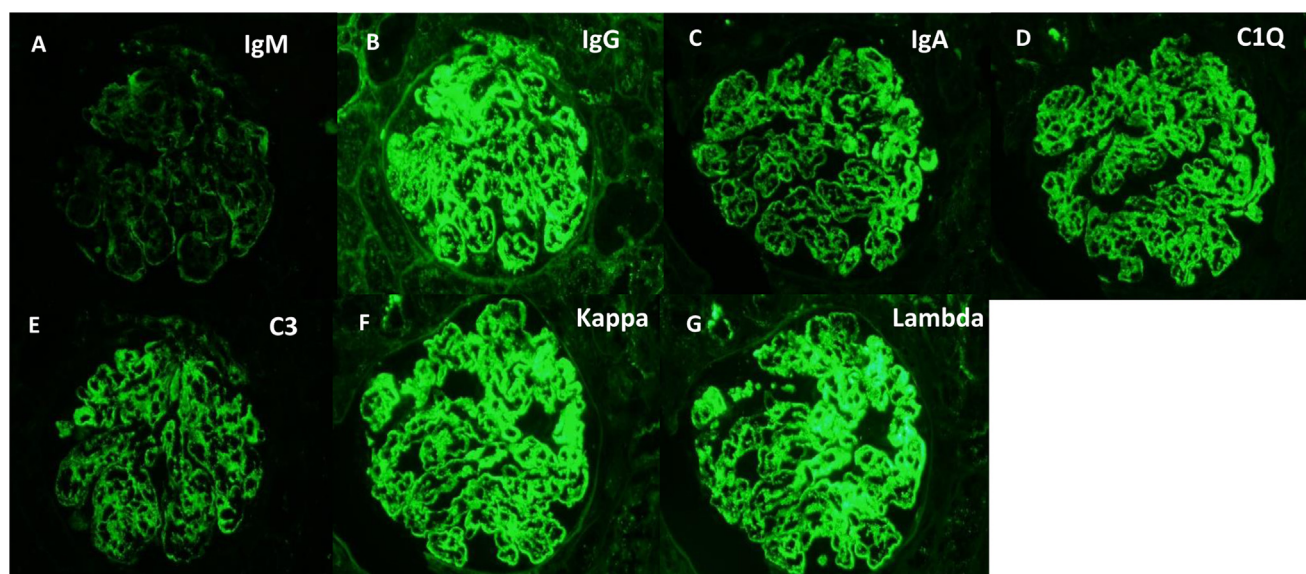


Figure 5. Immunofluorescence (IF) staining in lupus nephritis. (A-F) IF findings from a patient with LN with a full house pattern. Abbreviation: IgM, immunoglobulin M.

Hydroxychloroquine is the most commonly prescribed antimalarial in SLE. It is well tolerated but rarely, and usually at high doses, hydroxychloroquine can cause pigment changes in the macula of the retina that can cause vision loss if unrecognized. Risk factors for hydroxychloroquine-associated vision loss include daily dose > 400 mg/d or cumulative dose > 1,000 g, underlying retinal or macular disease, age older than 60 years, and underlying kidney or liver disease (drug is eliminated by both routes). A dose of 5 mg/kg per day (maximum, 400 mg/d) is recommended for patients with SLE. Patients should have a baseline eye examination and evaluations every 12 months by an ophthalmologist to monitor for retinal toxicity.

Management of Proliferative LN: Induction Therapy

An algorithmic approach to the management of proliferative LN (class III, IV, or III/IV +V) is shown in Fig 3. This involves high-dose corticosteroids and either MMF or cyclophosphamide (Table 3). These induction regimens are generally accepted as SOC and are supported by evidence from RCTs. However, despite the supporting evidence, none of these drugs are approved by the US Food and Drug Administration (FDA) and their use in LN is

considered off label. With the exception of corticosteroids, there are no FDA-approved therapies for LN.

Cyclophosphamide (oral or IV) has been used as SOC for LN induction since the original NIH study done in the 1980s. In this study, the addition of IV cyclophosphamide to corticosteroid treatment improved kidney outcomes and reduced kidney failure risk beyond corticosteroids alone after several years of follow-up. Cyclophosphamide is associated with significant toxicity, specifically increasing the risk for premature ovarian failure and future malignancy. This has led to efforts to reduce cyclophosphamide exposure and find alternative induction regimens with a better safety profile.

ELNT compared the standard-dose (NIH) regimen cyclophosphamide (0.5-1 g/m² monthly pulses for 6 months, total dose exposure of 9-12 g) with a low-dose IV cyclophosphamide regimen of 500 mg every 2 weeks for 6 doses (total dose exposure of 3 g). Outcomes were measured at 1 year with 10-year follow-up. The 2 regimens were equally effective for short-term remission induction (54% remission for low-dose vs 46% in high-dose cyclophosphamide at 1 year) and long-term renal preservation. There were fewer adverse events in patients treated with low-dose cyclophosphamide. This study was performed in a predominantly white population, but more recent RCTs using this low-dose strategy also suggest efficacy in multiethnic LN populations.

The Aspreva Lupus Management Study (ALMS) was a multiethnic prospective study of 370 patients that compared MMF (3 g/d) with NIH-regimen cyclophosphamide for LN induction and demonstrated equal efficacy at 6 months and after 3.5 years. Total (CR plus PR) response was 56% in the MMF group (8.6% CR) and 53% in the cyclophosphamide group (8.1% CR) at 6 months. CR rates increased and remained similar between groups (62% for the MMF group and 59% for the cyclophosphamide group) after 3.5 years of treatment. Adverse event rates were similar between groups, but gastrointestinal toxicity and the overall dropout rate was higher in the MMF-treated group. However, MMF does not increase the risk for infertility or malignancy like cyclophosphamide and has now largely replaced cyclophosphamide as the first-line therapy for the induction phase.

Taking all these trials together, either low-dose cyclophosphamide or MMF may be considered acceptable options as first-line induction therapy for proliferative LN. A direct comparison of low-dose cyclophosphamide to MMF in a South Asian LN cohort found similar 6-month renal response rates. Thus, our approach to LN induction therapy is to treat with either MMF or low-dose cyclophosphamide and reserve NIH-regimen cyclophosphamide or oral cyclophosphamide for severe or resistant cases.

Management of Proliferative LN: Maintenance Therapy

Attaining a CR by the end of induction therapy is not common in LN. Furthermore, relapses are common and

Table 3. Induction and Maintenance Treatment Regimens for Management of Proliferative Lupus Nephritis

Medication Name	Treatment Regimen	Dosing
LN Induction: First-Line Therapies		
CYC	IV CYC (NIH)	0.75-1 g/m ² monthly × 6 doses; reduce dose by 25% for GFR < 20 mL/min
	IV CYC (low dose) ^a	500 mg every 2 wk × 6 doses
	Oral CYC	1.5 mg/kg/d × 3-6 mo; reduce dose by 25% for GFR < 20 mL/min
MMF or mycophenolate sodium (myfortic)	Oral MMF ^a	MMF: 1,000-1,500 mg 2×/d × 6 mo Myfortic: 720 mg 2×/d × 6 mo
LN Induction: Emerging Therapies		
Rituximab	IV rituximab	1,000 mg on d 1 and 14 × 2 doses
Multitarget regimen	Tacrolimus or cyclosporine plus MMF	0.05 mg/kg/d tacrolimus (target trough level 4-6 ng/mL) or 3-5 mg/kg/d cyclosporine (level is not well established) plus MMF 500-1,000 mg 2×/d × 6 mo
LN Maintenance Regimens		
MMF ^a	—	500-1,000 mg 2×/d ^b
Azathioprine	—	1.5-2 mg/kg/d

Abbreviations: CYC, cyclophosphamide; GFR, glomerular filtration rate; IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; NIH, National Institutes of Health.

^aFirst-line treatment choice for induction and maintenance therapy.

^bThe optimal duration of maintenance therapy is unclear; however, a minimum of 24 months is commonly required.

are associated with increased risk for progressive chronic kidney damage. Therefore, the purpose of maintenance therapy is 2-fold: (1) consolidate responses into durable complete remissions without the toxicity of induction regimens, and (2) continue suppression of autoimmunity to prevent LN flare. MMF or azathioprine are commonly used for maintenance therapy in LN (Fig 3; Table 3). The use of these agents is based on studies that demonstrated maintenance with azathioprine or MMF is more effective and less toxic than maintenance with quarterly doses of IV cyclophosphamide in preventing kidney failure or death. These agents were also directly compared in 2 RCTs. In a predominantly white population (the MAINTAIN nephritis trial, $n = 105$), there was no difference in time to first renal flare between MMF and azathioprine. However, in a multiethnic study (ALMS maintenance trial, $n = 227$), MMF (2 g/d) was found to be superior to azathioprine (2 mg/kg per day) in preventing treatment failure (16.4% vs 32.4%, respectively; $P = 0.003$) defined as a composite end point of death, kidney failure requiring KRT, doubling of serum creatinine level, LN flare, or need for rescue therapy. MMF has become the therapy of choice for LN maintenance in most cases. However, azathioprine remains an acceptable alternative and is preferred in specific situations, such as pregnancy, for which azathioprine can be safely used but MMF is contraindicated. Before initiating azathioprine treatment, we recommend checking thiopurine methyltransferase (TPMT) activity. Genetic mutations causing TPMT deficiency are reported to be as high as 6 per 1,000 persons. Azathioprine use should be avoided in the setting of TPMT deficiency because it can lead to potentially life-threatening bone marrow toxicity at usual doses.

The optimal duration of maintenance therapy is unclear and not evidence based. Durations of 12 to 36 months have been studied in clinical trials and guidelines largely based on expert opinion suggest that maintenance therapy should be continued for at least 12 to 18 months after CR has been achieved. There is even less guidance in the setting of persistent PR, and in these cases, a repeat kidney biopsy may be needed to avoid over- or underimmunosuppression, as described previously (Fig 3). Finally, treatment may need to be continued indefinitely in some patients and should be considered based on disease severity and relapse risk for that individual.

Role of Corticosteroids in the Management of LN

Corticosteroids are effective in rapidly controlling inflammation but are also associated with considerable treatment-associated toxicity (Box 1). These adverse events are largely time and dose dependent, but the optimal dosing and duration of corticosteroid administration in LN is poorly defined and guided by limited evidence. Therefore, corticosteroids are likely overused in the management of LN and although no clinical trial has directly compared high- to low-dose corticosteroid therapy in LN, observations from several recent trials suggest that limiting

Box 1. Complications Associated With Corticosteroid Use

Side Effects

- Infection
- Weight gain
- Swelling
- Blurry vision
- Insomnia
- Acne, hirsutism
- Facial swelling
- Depression/anxiety
- Sudden mood swings
- Easy bruising
- High blood pressure

Consequences of Side Effects

- Medication intolerance
- Polypharmacy; additional medications needed to control side effects attributed to corticosteroids increases medication burden
- Poor medication adherence
- Increased cost of care

Chronic Damage

- Obesity
- Type 2 diabetes mellitus
- Cataracts/glaucoma
- Muscle atrophy
- Avascular necrosis
- Osteoporosis

Consequences of Chronic Damage

- Chronic debilitating comorbid conditions
- Increased cardiovascular risk

cumulative corticosteroid burden may not negatively affect LN response rates. For example, in a prospective pilot study of 50 patients with class III, IV, or V LN, oral corticosteroids were not used during induction. Instead patients received rituximab and MMF plus 2 boluses of IV methylprednisolone (500 mg each). After 12 months, 52% of patients achieved CR, comparable to previously reported LN response rates using standard high-dose corticosteroid therapy. This suggests that the traditional approach to LN management may overexpose patients to corticosteroids, increasing toxicity risk without adding benefit. Though concrete recommendations cannot be made until further support is provided from large prospective clinical trials, we suggest that close attention be paid to the dose and duration of corticosteroid therapy in the management of LN. Complete corticosteroid withdrawal should be attempted in all patients who achieve a clinical response. Our approach to corticosteroid use in the management of proliferative LN is shown in Figure 5.

Returning to question 4, the correct answer is (b). LN is a relapsing disease and long-term immunosuppression is often warranted. The optimal duration of immunosuppression is not currently known. Regarding (a), MMF has

not been shown to be superior to cyclophosphamide in large randomized controlled studies. Hydroxychloroquine is essential to management because it is associated with improved response and less disease relapse. Hydroxychloroquine should be used as a part of LN management; thus (c) is wrong. Answer (d) is incorrect because rituximab has not been shown to improve LN outcomes in large RCTs.

Additional Readings

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Emerging Therapies in LN

The current approach to LN management has significant room for improvement. Renal outcomes remain suboptimal and multiple promising therapies have failed in clinical trials. Despite these setbacks, several novel drugs are currently under evaluation (Table 4). B-Cell depletion and multitarget therapy (MTT) with calcineurin inhibition are already being used in clinical practice for select LN populations, albeit off label.

B-Cell Depletion in LN

The excitement for targeting B cells stems from observational studies that showed improved clinical response after B-cell depletion with rituximab, a monoclonal antibody against CD20, in patients with LN. Unfortunately, the phase 3 Lupus Nephritis Assessment With Rituximab (LUNAR) Study failed to show that rituximab added to SOC was superior to SOC alone.

Despite this result, rituximab is still commonly used in the management of LN, especially refractory LN, and several clinical trials are currently underway to address questions that emerged from LUNAR. For example, a phase 2 study is evaluating whether more potent B-cell depletion may be required for LN. In this 2-year study, a combination of SOC and obinituzumab, a type II anti-CD20 monoclonal antibody that has shown superiority to rituximab (a type I drug) in depleting tissue B cells in lymphoma, is being compared to SOC alone (ClinicalTrials.gov identifier NCT02550652). Circulating B-cell activating factor (BAFF) is overexpressed at LN flare and suppression of BAFF with belimumab, a humanized monoclonal antibody against BAFF and FDA approved for nonrenal SLE, is being evaluated in 2 prospective RCTs to determine its ability to improve LN response and limit flare beyond SOC (ClinicalTrials.gov identifiers NCT01639339 and NCT02260934).

The ultimate role of B-cell depleting therapy in LN is yet to be determined and will be guided by results of

Table 4. Active Clinical Trials in LN

Drug Name	MOA	Phase	Sponsor
Voclosporin	Calcineurin inhibitor	3	AURA-LV; Aurinia Pharmaceuticals
Obinituzumab	Monoclonal anti-CD20	3	Nobility; Roche
Anifrolumab	IFN- α receptor blocker	2	TULIP-LN; AstraZeneca
Belimumab	Anti-BAFF	3	BLISS-LN; Glaxosmithkline
Belimumab plus rituximab	B-Cell depletion + BAFF suppression	2	ITN-CALIBRATE; Immune Tolerance Network
CFZ533X2202	Anti-CD40-CD40L	2	Novartis
BMS-986165	Tyrosine kinase 2 inhibitor, blocks IL-12/23, interferon	2	Paisley-LN; Bristol-Squibb Myers
KZR-616	Targeted inhibition of immunoproteasome	2	Kezar Pharmaceuticals

Abbreviations: BAFF, B-cell activating factor; IFN- α , interferon α ; IL-12, interleukin 12; MOA, mechanism of action.

these clinical trials. Until then, B-cell depletion with rituximab may be considered in cases of disease resistance and as a maintenance therapy to help prevent disease relapse in patients intolerant or refractory to MMF or azathioprine.

Multitarget Approach in LN

Calcineurin inhibitors (CNIs) have been studied extensively in LN. Perhaps the most compelling studies involve combining CNI with MMF and corticosteroids in an MTT approach. A prospective study of 302 Chinese patients compared 6 months of MTT with tacrolimus (4 mg/d) and MMF (1 g/d) with NIH-regimen cyclophosphamide. The MTT group demonstrated superior 6-month CR rates compared with NIH-regimen cyclophosphamide (46% vs 26%, respectively; $P < 0.001$). However, during the 18-month follow-up, CRs were equal for both groups. This study highlights the danger of using short-term response to infer long-term outcomes, especially when a CNI is involved. CNIs reduce proteinuria by nonimmune mechanisms and because renal response is largely determined by improvements in proteinuria, results must be interpreted cautiously. This study also raises the question of whether proteinuria should be used as a marker of clinical response to CNIs.

The Auricular Lupus Nephritis (AURA-LV) phase 3 study will attempt to answer some of these questions in a multiethnic population. In this study, voclosporin, a novel cyclosporine derivative with a more stable pharmacokinetic profile, plus SOC (MMF, 2 g/d, with reduced-dose prednisone) will be compared with SOC alone. This study is based on a recent phase 2 trial that showed superior 6- and 12-month response rates with voclosporin plus SOC. The positive result is tempered by a higher frequency of adverse events in the voclosporin group with a significantly higher mortality rate in the low-dose voclosporin group compared with placebo and high-dose voclosporin (11.2% vs 1.1% and 2.2%, respectively). Demonstrating safety in addition to efficacy will be critical to the phase 3 study. Finally, repeat kidney biopsies will be done in a subset of patients at the end of this 2-year study. Demonstrating improvement in histologic disease activity with MTT beyond SOC would provide confidence that CNIs are suppressing autoimmunity and not just masking disease hemodynamically.

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dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int*. 2019;95(1):219-231. ★ **ESSENTIAL READING**

Management of Class V LN

Immunosuppression is recommended for patients with class V (membranous) LN with nephrotic-range proteinuria and/or a GFR decline. Unlike primary membranous nephropathy, class V does not typically remit spontaneously. Treatment with immunosuppression is generally reserved for patients with associated nephrotic-range proteinuria due to known risk for developing progressive chronic kidney disease (including kidney failure) if left untreated. Patients with sub-nephrotic-range proteinuria may still warrant immunosuppression to treat class V LN. It is our view that immunosuppression should be considered for patients with class V LN and persistent protein excretion > 1 g/d. The rationale for this view is that protein excretion < 0.8 g/d at 1 year was associated with a favorable long-term outcome in patients in ELNT, which included patients with mixed proliferative and membranous LN. In addition, several studies have demonstrated comparable long-term outcomes in patients with pure class V and mixed (class III/IV + V) LN, suggesting a more aggressive treatment approach is needed for patients with pure class V LN.

Class V LN occurs less frequently than proliferative LN and well-powered RCTs of treatment options are lacking. Treatment recommendations have largely been based on single-center cohort studies or trials that included a mix of patients with membranous and proliferative LN. Although several regimens have been proposed, the optimal course of treatment for class V is not known. A small RCT demonstrated that NIH-regimen cyclophosphamide or cyclosporine were better than corticosteroids alone. MMF was found to be comparable to NIH-regimen cyclophosphamide after subgroup analysis from 2 prospective studies. MMF is commonly used as first-line therapy for class V LN but this is more due to familiarity than superiority over other agents. Importantly, the currently available evidence supports the use of MMF, CNIs, or cyclophosphamide for treatment of class V LN. [Figure 6](#) provides an algorithmic approach to the management of class V LN.

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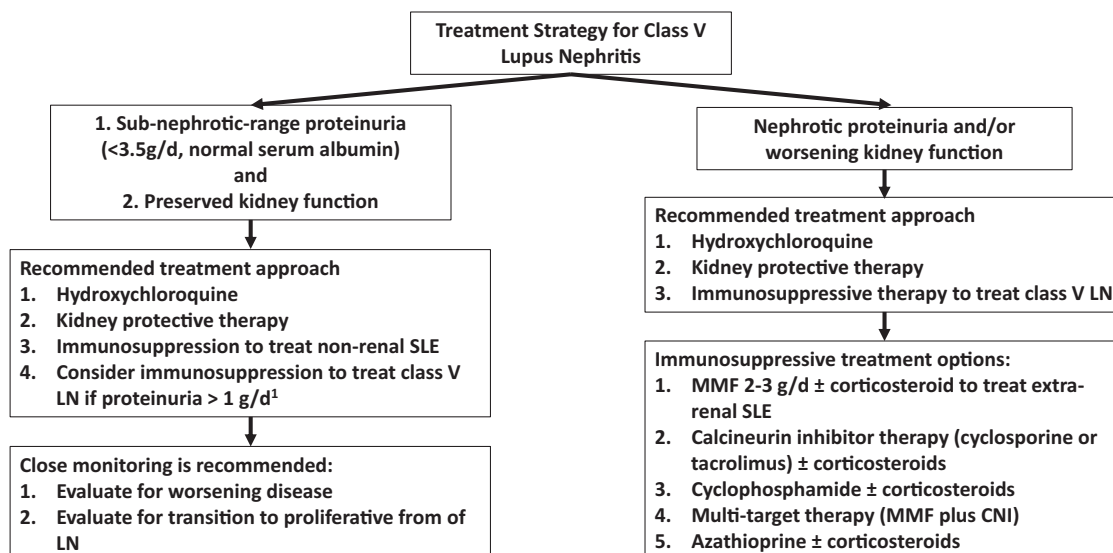


Figure 6. Treatment of membranous lupus nephritis (LN). An approach to management of class V LN. If proteinuria is sub-nephrotic range and serum creatinine is normal, antiproteinuric, antihypertensive, and antimalarial therapies should be used for the LN and immunosuppressive therapies for extrarenal lupus as indicated. If proteinuria is nephrotic range and/or glomerular filtration rate (GFR) is decreased, immunosuppression with any of the agents listed should be initiated. Mycophenolate mofetil (MMF) is commonly used first line. ¹The prevailing approach according to expert opinion for the management of class V LN is to reserve immunosuppressive therapy for nephrotic syndrome and/or worsening GFR. Because class V LN does not typically remit spontaneously, it is our approach to consider immunosuppression for persistent protein excretion > 1 g/d. Abbreviations: CNI, calcineurin inhibitor; SLE, systemic lupus erythematosus.

Pregnancy and LN

Case 5: A 27-year-old woman with a history of recurrent LN that has been in complete remission for the past year presents for prepregnancy counseling. She has a creatinine level of 1.1 mg/dL and urine protein excretion of 0.9 g/d.

Question 5: Based on the current evidence, how would you counsel this patient?

- Previous renal flares, presence of APLAs, urine protein excretion > 1 g/d, and Hispanic ethnicity are all associated with poor fetal outcomes in LN
- Use of hydroxychloroquine is not recommended
- Pregnancy is not associated with increased risk for lupus flare
- MMF can be safely continued during pregnancy

For the answer to the question, see the following text.

Patient with LN who want to have children should be counseled to wait until LN is quiescent for at least 6 months. Patients should be switched to a “pregnancy-friendly” regimen at least 3 months before attempting conception. Patients taking MMF should be switched to azathioprine. CNIs can be continued throughout pregnancy. The safety of rituximab in pregnancy is not very well established but the manufacturer’s label warns against conception for a year after rituximab use. Rituximab can

cross the placenta and cause fetal B-cell depletion. Tapering immunosuppressive therapy and attempting to conceive at the same time is strongly discouraged because getting pregnant with active disease has deleterious consequences. However, >80% of pregnancies in patients without active LN or extrarenal lupus activity are uncomplicated. A prospective cohort study of 71 pregnancies in patients with mostly quiescent LN, optimally managed with prepregnancy counseling by a multidisciplinary team, found that LN flares occurred in 20% of patients; preeclampsia or HELLP (hemolysis, elevated liver enzyme levels, and a low platelet count) syndrome, in 11%; fetal loss, in 8.4%; and preterm birth, in 30.8%. In comparison, the fetal loss rate after 20 weeks of gestation in the general US population is reported to be 6 in 1,000 live births and preterm birth occurs in ~10% of pregnancies.

Treating a renal flare in pregnant patients can be challenging. A kidney biopsy may be needed to establish the diagnosis and can be performed safely up to 20 weeks of gestation. Therapeutic options are limited and include hydroxychloroquine, corticosteroids, azathioprine, CNIs, and IV immune globulin. The authors typically use a multitargeted regimen of azathioprine and CNIs that are combined with steroids. IV immune globulin is reserved for resistant and/or severe cases. Hydroxychloroquine should be used in all pregnant patients with SLE unless contraindicated. Hydroxychloroquine use has been shown to reduce the probability of having a small-for-gestational

age baby by 85% and reduces the risk for congenital heart block by 50% in babies of mothers who are anti-Ro antibody positive. In addition to hydroxychloroquine, treatment with azathioprine and/or a CNI may most effectively treat LN and is recommended as a first-line treatment option in the setting of renal flare during pregnancy. Corticosteroids, while effective, increase the risk for gestational diabetes and use should be limited if possible.

For question 5, the correct answer is (a). In a prospective observational cohort of pregnant patients with SLE, a history of LN, presence of APLAs, protein excretion > 1 g/d, and Hispanic ethnicity have all been found to be associated with worse fetal outcomes. In contrast, the use of hydroxychloroquine reduces flares, infections, and thrombosis and is associated with better renal survival over the long term. Pregnancy is associated with increased risk for lupus flare and disease should be quiescent for at least 6 months before considering pregnancy. MMF is contraindicated in pregnancy because it is teratogenic.

Additional Readings

- Buyon JP, Kim MY, Guerra MM, et al. Predictors of pregnancy outcomes in patients with lupus: a cohort study. *Ann Intern Med.* 2015;163:153-163. ★ **ESSENTIAL READING**
- Moroni G, Doria A, Giglio E, et al. Maternal outcome in pregnant women with lupus nephritis. A prospective multicenter study. *J Autoimmun.* 2016;74:194-200. ★ **ESSENTIAL READING**

Dialysis and Transplantation in LN

LN accounts for ~2% of the population of patients receiving KRT in the United States. According to the US Renal Data System database, the incidence of kidney failure requiring KRT attributed to SLE is 3 to 4 per million per year. Though this risk has largely been stable during the past 2 decades, substantial disparities have been described in certain populations. Patients of younger age, female sex, African ancestry, lower socioeconomic status, and limited access to care and those residing in the Southeastern United States have been described to be at higher risk. The risk for kidney failure is at least 4-fold higher in patients of African ancestry compared with other ethnicities.

Patient with LN who reach kidney failure are candidates for all modalities of KRT but are historically less likely to undergo preemptive kidney transplantation or be offered peritoneal dialysis than patients with primary glomerular diseases. Patients with LN treated with dialysis have comparable 5-year survival rates as patients without LN receiving dialysis. Patients with LN who receive a kidney transplant have better survival and fewer cardiovascular and infectious complications than patients with LN receiving dialysis. In one study of mortality and KRT, about 32 events per 1,000 patient-years occurred in 946 patients with LN who underwent transplantation

compared with about 257 events per 1,000 patient-years in 3,431 patients with LN receiving dialysis. Conventional wisdom has suggested that patients with LN receive several (3-6) months of dialysis before a kidney transplant to ensure disease quiescence. However, a study of more than 4,700 patients with LN showed that a wait time on dialysis of more than 3 months was associated with 2-fold increased risk for graft failure compared with those with fewer than 3 months receiving dialysis. Patients with LN who underwent preemptive transplantation had superior allograft and overall survival and did not have increased risk for recurrent LN posttransplantation.

LN may recur in kidney allografts with an estimated incidence of 2% to 11% after a median duration of 4 years. Recurrence is most commonly class II LN, and although recurrence increases risk, graft loss is rare and patient and allograft survival are similar in patients with and without LN. Antiphospholipid syndrome increases the risk for allograft loss and because it occurs frequently in LN, it should be screened for before transplantation.

Thus, due to the substantially reduced morbidity and mortality and generally favorable outcomes, the KRT of choice for patients with LN who require it is kidney transplantation. Efforts should be made to consider patients with LN for preemptive transplantation and not to delay transplantation for those receiving dialysis.

Additional Readings

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- Sabucedo A, Contreras G. ESKD, transplantation and dialysis in lupus nephritis. *Semin Nephrol.* 2015;35(5):500-508. ★ **ESSENTIAL READING**
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Improving Outcomes in LN

The ultimate goal of treatment in LN is to prevent progressive kidney damage and kidney failure. Minimizing LN flares and early identification of flare when it occurs are critical to preserving long-term kidney health. Chronic damage accumulates quickly and repeated flares are associated with progressive chronic kidney disease.

The current approach to LN management treats all patients similarly. However, LN is a heterogeneous disease with multiple dysregulated immune processes contributing to the development and maintenance of disease.

Determining which pathways are driving disease in an individual patient at the time of flare is an essential first step toward personalizing treatment. This will most likely be accomplished by combining clinical data with molecular and genetic data from the individual. To this end, efforts are underway to add more information to the histology of the kidney biopsy through “omic” analyses of kidney tissue and to identify biomarkers of active pathogenic pathways in serum and urine of patients with SLE and LN.

Conclusions

Despite significant advances in our understanding of LN pathogenesis, only modest progress has been made in improving our ability to treat and improve outcomes in LN. Patients with SLE with LN continue to be at high risk for significant morbidity and mortality. Furthermore, kidney failure rates remain unacceptably high. Looking forward, improving outcomes in LN will require a multifaceted approach to LN management. New clinical trial design, identification of novel disease markers that allow for earlier disease recognition, and patient stratification and identification of a variety of effective and targeted therapies will be needed to improve long-term LN outcomes. Correlating molecular expression data with clinical and morphologic features present in individual

patients with LN may help accomplish this goal and lead to a more personalized approach to LN management in the future.

Article Information

Authors' Full Names and Academic Degrees: Samir V. Parikh, MD, Salem Almaani, MD, Sergey Brodsky, MD, and Brad H. Rovin, MD.

Authors' Affiliations: The Ohio State University Wexner Medical Center, Columbus, OH.

Address for Correspondence: Brad H. Rovin, Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, OH 43210. E-mail: rovin.1@osu.edu

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