

# The Shifting Landscape of Lupus Nephritis Management: A Review

Adegbenga A. Bankole<sup>1</sup>, Jane N. Nwaonu<sup>1</sup>

1. Rheumatology, Virginia Tech Carilion School of Medicine (VTCOSM), Roanoke, USA

**Corresponding author:** Adegbenga A. Bankole, aabankole@vt.edu

Review began 12/30/2021

Review ended 12/30/2021

Published 01/05/2022

© Copyright 2022

Bankole et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

---

## Abstract

Systemic lupus erythematosus (SLE) is commonly the first autoimmune disease that comes to mind for most people when rheumatology is mentioned. It remains an enigma that many of us, including patients and healthcare providers, do not fully understand. Although an ancient disease, it still remains difficult to both diagnose and treat. Historically, there has always been a paucity of therapeutic interventions for SLE as a whole. One of the most distressing manifestations for the patient and diagnostic and therapeutically challenging aspects of SLE is lupus nephritis (LN). There has historically been some difficulty in the development of LN drugs that provide significant therapeutic benefits while having an acceptable side-effect profile. This difficulty led to decades in which no drugs were approved for LN. With a better understanding of the pathogenesis of SLE and LN and improvement in trial design, great therapeutic strides have recently been made. The immunosuppressive landscape of LN has changed recently with the approval of two newer agents as well as a number of promising trials in LN. With the increased number of therapeutic agents (both immunosuppressive and non-immunosuppressive), the clinical question is how and when to use these medications, and, more importantly, which agents to use first. With the increased number of agents, the answers to these questions are becoming more difficult to answer. The purpose of the paper is to review updates in LN diagnosis and management.

---

**Categories:** Nephrology, Rheumatology, Therapeutics

**Keywords:** systemic lupus erythematosus, lupus nephritis, lipid disorders, immune, acute tubulointerstitial nephritis, kidney disease, immune mediated side effects, anti-nuclear antibody, auto immune, systemic reviews

## Introduction And Background

Systemic lupus erythematosus (SLE) is the archetypical example of an autoimmune disease. It is a clinically and serologically diverse disease that can affect multiple different organs and therefore presents with a variable array of manifestations [1]. Given this, it is sometimes called the great masquerader. Despite the wide range of symptoms, there are well-validated diagnostic tools and criteria used in arriving at a diagnosis of SLE [2]. The incidence and prevalence vary around the world with the highest estimates in North America (23.2/100000 person-years and 241/100 000, respectively) while the lowest incidence is in Africa and Ukraine (0.3/100000 person-years) [3]. Younger women of color are more frequently affected, including African Americans, Hispanics, and Asians, who have the highest incidence and prevalence of SLE in the United States [4]. Patients with SLE suffer significant health risks and have been shown to have nearly double the premature mortality risk of healthy controls [5].

Clinically, SLE can vary from mild disease with musculoskeletal or cutaneous involvement to more severe organ manifestations affecting the renal, central nervous, and cardiovascular systems. Lupus nephritis (LN) is one of the more frequent and most severe manifestations of SLE [6]. The clinical update by Imran et al. noted that around 15%-30% of the patients with lupus were found to have LN at the time of initial diagnosis and 30%-50% developed LN during the course of the disease. This makes LN both a common and severe manifestation of SLE, resulting in significant morbidity and mortality. LN has a cause-specific standard mortality rate (SMR) of 4.689 compared to other complications, including cardiovascular disease SMR of 2.253, and infection SMR of 4.980 [7]. LN also carries a significant risk of end-stage renal disease and all the associated comorbidities [8].

The presentation of LN is variable and may include fatigue, hypertension, edema, proteinuria, abnormal urinary sediment, and abnormal renal function. The clinical picture is divided into nephritic or nephrotic syndrome, though a significant overlap between the two occurs [9]. Laboratory testing, such as urinalysis and microscopy, and immunological parameters can point toward renal involvement and can determine between nephritic and nephrotic disease. A renal biopsy is needed to confirm the diagnosis, to help guide treatment, and even to determine treatment response. LN was first classified histologically by the World Health Organization (WHO) in 1975 [10] and then updated in 1978 [11]. In 2003, the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis was published [12] and this was updated in 2018 [13].

Lupus nephritis is confirmed when there is a positive biopsy in the presence of a positive antinuclear

### How to cite this article

Bankole A A, Nwaonu J N (January 05, 2022) The Shifting Landscape of Lupus Nephritis Management: A Review. Cureus 14(1): e20950. DOI 10.7759/cureus.20950

antibody (ANA) test and/or anti-double-stranded DNA (anti-dsDNA) antibody [2]. Some findings on biopsy, including intense C1q staining, full-house staining, extraglomerular deposits, subendothelial and subepithelial deposits, and tubuloreticular inclusions are very specific for LN and are helpful for confirming the diagnosis [14]. LN can be classified into six histologic groups based on the ISN/RPS classification criteria [12]. These classification groupings have clinical relevance and tend to correspond to the two clinical classes (Table 1). The histological groups have a significant impact on therapeutic choices and treatment goals and are of prognostic value. The biopsy findings of the nephritic syndrome are mostly consistent with LN classes II-IV with those of LN class V being of nephrotic syndrome. As LN classes III and IV carry a 22% risk of end-stage renal disease (ESRD) [8], they tend to be more aggressively managed. The management of LN is divided into the induction and maintenance phases. The goal of induction is to control intrarenal inflammation and immune-mediated activity as rapidly as possible, thereby limiting further parenchymal damage. Maintenance therapy consolidates this and prevents relapse and reactivation of autoimmunity [15].

Classification of glomerulonephritis in systemic lupus erythematosus			
	Histology	Presentation	Proteinuria Goal
<b>Class I</b>	Minimal mesangial LN	Asymptomatic/Nephritic	<500 mg/24 hours
<b>Class II</b>	Mesangial proliferative LN	Asymptomatic/Nephritic	<500 mg/24 hours
<b>Class III</b>	Focal LN	Nephritic	<500 mg/24 hours
<b>Class IV</b>	Diffuse LN	Nephritic	<500 mg/24 hours
<b>Class V</b>	Membranous LN	Nephrotic	<1000 mg/24 hours
<b>Class VI</b>	Advanced sclerosing LN	End-stage renal disease	Not applicable

**TABLE 1: Classification of glomerulonephritis in systemic lupus erythematosus**

Given the potential complications, repeating a renal biopsy can be frightening to both the patient and the care provider but can be of great value. A repeat biopsy has been shown to further direct therapy ensuring appropriate treatment while avoiding excessive immunosuppression [16]. Though there is no agreed-upon timing for a second biopsy, the patients should be in complete renal remission for at least 12 months before it is done, as a biopsy at that time will help guide maintenance immunosuppression [17]. It may also be helpful in determining incomplete response to therapy and risk of relapse especially as the clinical and serological activity may not reflect the histological activity seen on the biopsy [17].

## Review

### Clinical features

The diversity of the clinical presentations of LN ranges from asymptomatic hematuria/proteinuria, hypertension, overt nephritic and nephrotic syndromes, rapidly progressive glomerulonephritis, and ESRD needing renal replacement therapy. LN, like other more severe manifestations of SLE, is more common in African Americans, Asian/Pacific Islanders, and Hispanic patients [8,18]. LN is a major predictor of morbidity and mortality and may result in the need for renal replacement therapy [8]. Any part of the kidney can be affected by SLE, but the commonest site of renal pathology is the glomerulus [12,19]. The clinical features, treatment, and prognosis vary depending on the site of the pathology. Patients may be asymptomatic, have massive proteinuria, or have rapidly progressive glomerulonephritis leading to ESRD [15].

LN with a nephrotic syndrome commonly presents with proteinuria, peripheral edema, hypoalbuminemia, and dyslipidemia [20]. The levels of hypercholesterolemia and hypoproteinemia/hypoalbuminemia reflect the levels of disease activity in such patients. Studies have shown an association between autoantibodies like anti-dsDNA, anti-histone, and anti-nucleosome antibodies and nephrotic syndrome correspond histologically to ISN/RPS class IV and V [21]. LN with the nephritic syndrome can present with periorbital and pedal edema, hematuria, and non-nephrotic range proteinuria [22] and corresponds most closely to (ISN/RPS class III and IV). As a result of the heterogeneity in the clinical symptoms of LN, the clinical picture may not always correlate with the pathological findings. Other clinical findings can include hypertension, oliguria, and renal insufficiency.

Though not often recognized, dyslipidemia is related to alterations in lipid and lipoprotein metabolism [23]. There is a deficiency and dysfunction of lipoprotein lipase activity, an increased expression of enzymes like acetyl-CoA carboxylase and fatty acid synthase that cause increases in the production of lipids, as well as a downregulation of hepatic lipase activity that results in reduced fatty acid catabolism in the liver [24]. This dyslipidemia also increases the risk of thrombosis in SLE patients who are already predisposed to

coagulopathy and can often present as renal vein thrombosis (RVT) and pulmonary embolism [25]. RVT in LN is more commonly associated with membranous lupus nephritis and to a lesser extent with proliferative glomerulonephritis [26]. RVT has also been associated with antiphospholipid syndrome in patients with SLE, and here it can be arterial or venous [27]. As there are no pathognomonic clinical features beyond vague flank pain [28], we should think of RVT if there is an acute worsening in proteinuria, and renal doppler ultrasonography studies can be helpful in arriving at the diagnosis [26], although spiral CT, MRA, and selective venography have a better sensitivity [29]. Although the pathogenesis of renal vein thrombosis in LN remains obscure, nephrotic syndrome is associated with changes in concentrations of factors V, VII, VIII, and X, fibrinogen, and platelets, which result in a hypercoagulable state [30-31].

## Autoantibodies

Autoantibody testing is the hallmark of autoimmune diseases, especially SLE and LN. They form part of the diagnostic criteria and can also have prognostic utility. Serum creatinine, glomerular filtration rate, proteinuria, and hematuria are already commonly used as part of the management of LN [32]. Combined with levels of anti-dsDNA antibodies and complements, they are good predictors of long-term renal outcome [33]. However anti-dsDNA antibodies and complements levels are not always abnormal in LN and do not always follow disease activity [34]. A low C4 may reflect a defect in the classical complement pathway and not SLE or LN activity. In fact, the low C4 is also a risk factor for the development of SLE and not just a marker of disease activity [35]. Complement C1q is the first subcomponent of the classical pathway of complement activation and is involved with clearing immune complexes and self-antigens generated during apoptosis [36]. An inherited deficiency in or low levels of C1q is associated with an increased risk of SLE and immune-mediated glomerulonephritis like LN [37]. Autoantibodies to C1q that lower the levels of C1q levels have been shown to closely correlate with LN disease activity levels [38]. Combining the results of the anti-dsDNA and anti-C1q antibody levels enhances the diagnostic specificity and sensitivity for concurrent SLE disease activity [39], and the absence of both anti-dsDNA and anti-C1q has a high negative predictive value for lupus activity.

A number of autoantibodies and serological tests correlate closely with renal pathology and LN disease activity. Anti-dsDNA, anti-nucleosome, anti-ribosome P, anti-C1q antibodies, and C3/C4 follow disease activity. A high titer of anti-C1q or anti-dsDNA antibodies can differentiate LN III and VI from LN V. Anti-C1q has demonstrated a relationship with proteinuria, and this may be higher in LN class V [40].

Antiphospholipid antibodies (aPL) are seen in patients with SLE and LN, and it is not clear that aPL alters the outcomes of LN [41]. However, aPL should be evaluated in all patients with SLE. Some autoantibodies like antibodies to M-type phospholipase A2 receptor (PLA2R) are used to rule out LN. The anti-PLA2R antibody is a specific marker of idiopathic membranous nephritis [42]. There are a number of novel autoantibody tests available that have not been incorporated into routine clinical care.

## Treatment

LN is treated with both immunosuppressive and non-immunosuppressive therapies in order to achieve full control. The ACR Task Force Panel on the management of LN recommends that addressing complications/clinical features like hypertension, proteinuria, and dyslipidemia with adjunctive therapy in addition to immunosuppressive therapy leads to the best outcomes [43]. Serum and urine biomarkers are used to monitor therapy, and there is a role for repeated biopsy in the management of LN [32].

Since the discovery of glucocorticoids (GC) in the 1930s-40s, they remain the first drug used in LN. When given at doses above the physiological glucocorticoid levels, they have both anti-inflammatory and immunosuppressive effects [44]. The mechanisms of action of GC are now better understood as genomic mechanisms involving receptor binding, translocation to the nucleus, and binding to DNA binding sites known collectively as glucocorticoid response elements [45], and non-genomic mechanisms of action via the inactivation of the phospholipase A2 enzyme [46]. There are various routes of administration and dosing protocols for glucocorticoids. Induction therapy with high-dose GC is generally accepted as the initial first step in the treatment of LN classes III, IV, and V, with the current, recommended starting doses of 0.5 to 1 mg/kg/d, followed by vaguely defined tapering schedules [47].

Although not a potent immunosuppressive agent, hydroxychloroquine (HCQ) should be used in all SLE patients, including patients with LN. HCQ is protective to the kidneys, reducing the progression of renal damage and SLE and LN flares [48]. As a result of these effects, HCQ remains recommended in the treatment of SLE and LN [49].

## Adjunctive therapy

Hypertension should also be addressed aggressively, as it can both be a symptom of LN and cause long-term renal disease. A renin-angiotensin-aldosterone system blockade is recommended in non-pregnant patients, as it has both antiproteinuric and antihypertensive effects [50]. Although all calcium channel blockers (CCBs) are equally effective in lowering blood pressure, non-dihydropyridine CCBs, such as diltiazem and verapamil, have the additional property of reducing proteinuria similar to angiotensin-converting enzyme

inhibitors(ACEI) as well as slowing the decline in renal function [51].

Statin therapy should be considered on the basis of lipid levels in the active phase of LN and long-term cardiovascular risk factors. Statins have been shown to reduce proteinuria and thus are a useful adjunct [52]. In addition, statins may have other non-lipid-related immunosuppressive benefits, such as reduction in serum immunoglobulin G (IgG), anti-dsDNA Abs, and proteinuria [53], and can improve long-term outcomes in SLE [54].

## Immunosuppressive therapy

Given the varied pathogenesis, presentation, and histology of SLE and LN, it is not surprising that until recently, there has been a lack of drug development resulting in Food and Drug Administration (FDA)-approved medications. After this dearth of new drugs being brought to the market for LN, there have been two medications approved since 2020. Both belimumab (B cell depletory) and voclosporin (a calcineurin inhibitor) are approved by the FDA for the treatment of adults with lupus nephritis.

As early as the 1980s, we understood that LN outcomes were improved with glucocorticoids, however, the dosing varied significantly between different groups. Various studies were performed [55] to determine the ideal dosing. For a number of years, the trend has been to use fewer glucocorticoids, and LN induction therapy is generally accepted as methylprednisolone between 250 mg to 1 g daily for three to five days followed by daily prednisone [56]. The response of LN to glucocorticoid therapy is complicated with multiple side effects and has led to the search for steroid-sparing therapies [57]. Over time, it was understood that a combination of glucocorticoid and immunosuppressive therapy was superior for induction. Intravenous cyclophosphamide (IV-CYC) quickly became the standard of care. Studies confirmed better outcomes in patients on IV-CYC plus glucocorticoids versus glucocorticoids alone [58]. IV-CYC is difficult to handle medically and was not always convenient for patients due to its route of admission, laboratory requirements, and side effects. This led to the search for other therapies and since 2005, it has been overall accepted that Mycophenolate mofetil (MMF) is the generally preferred agent for both induction and maintenance therapy in proliferative LN.

MMF showed superiority when compared to IV-CYC in its ability to induce remission and in its side-effect profile [59]. When compared with IV-CYC, MMF reduced the risk for renal failure, and this information supported the use of MMF as the first-line induction and maintenance therapeutic agent in LN [60]. MMF remains the cornerstone of LN treatment up until today. Ethnicity and even geographical region seem to have a significant role in the effectiveness of MMF in LN classes III-V, with MMF being more effective in African descent and Hispanic patients with LN when compared to IV-CYC [61]. MMF has been dosed at 2000 mg/day for six months followed by 1000 mg/day or 1000 mg three times daily [59,62]. Initially based on anti-rejection studies, it is currently accepted that patients of African descent benefit from the higher dose of 3000 mg/day [63]. There is still a role for induction therapy with IV-CYC for patients who do not achieve remission or low disease activity on MMF. There is a trend toward lower doses of IV-CYC (500 mg every 2 weeks X 6 doses), with long-term data confirming that these lower doses result in durable remission [64].

For the more difficult patients to treat, tacrolimus at a dose of 0.06-0.1 mg/kg/day can be used. When compared to MMF, tacrolimus is equivalent to the ability to achieve remission [65]. Tacrolimus, a calcineurin inhibition (CI), can be used in combination with MMF to further increase the rates of remission [66]. Given the side-effect profile of tacrolimus, it does need to have drug monitoring and should be kept within a narrow therapeutic index [67]. Voclosporin, another CI that is structurally similar to cyclosporine A has an improved pharmacokinetic profile compared to other CIs. It also does not affect the serum levels of MMF. Through the inhibition of calcineurin, voclosporin blocks IL-2 expression, reversibly inhibits T-lymphocytes and T-cell-mediated immune responses, and stabilizes podocytes in the kidneys. This, in turn, reduces inflammation and renal hemodynamics, treating and improving renal glomerulonephritis associated with SLE. It has shown both safety and superiority when used as part of a combination regimen [68]. Voclosporin can be used in combination with MMF as part of an induction protocol. It shows steroid-sparing properties and has a large effect on reducing proteinuria when dosed at 23.7 mg twice daily [68].

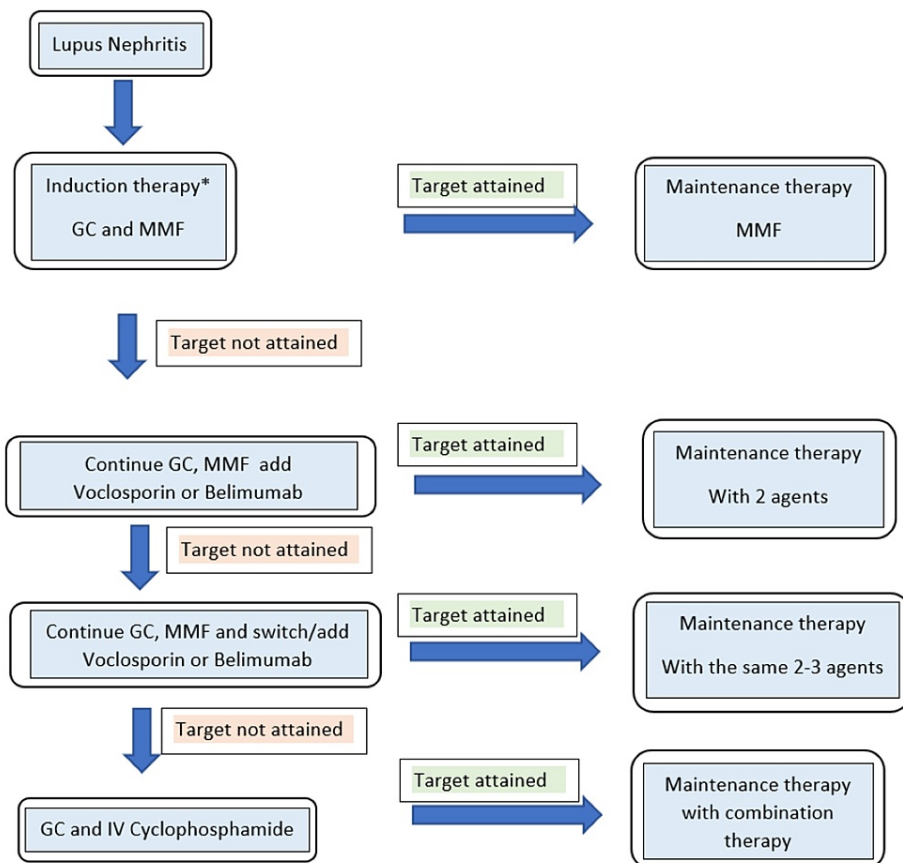
Maintenance therapy has been best studied with MMF and azathioprine (AZA), each having different advantages and disadvantages. MMF is superior to AZA in maintaining remission [69], with neither drug showing superiority in the side-effect profile. In the United States due to the teratogenic side effects, MMF has a black box warning regarding its use in pregnancy. For clinical use, there are now in place shared risk evaluation and mitigation strategies to ensure the safe use of MMF [70]. Patients who achieve remission of LN and wish to conceive or become pregnant should be transitioned to AZA given the safety in pregnancy and fact that flares of LN on AZA remain rare [71]. Belimumab is a recombinant human IgG-1 lambda monoclonal antibody that inhibits B-cell activating factors. It was approved by the FDA initially for the treatment of SLE, and subsequently also approved in December 2020 for the treatment of adults with active lupus nephritis [72]. The addition of Intravenous belimumab at a dose of 10 mg/kilogram of body weight to standard therapy over 104 weeks showed an increase in the number of patients who achieved a primary efficacy renal response [72].

At this time there is no current evidence to guide the choice between belimumab and voclosporin. However,

as voclosporin has renovascular benefits, it is a better choice in patients with nephrotic syndrome.

There are other therapeutics in various phases of investigation, including anifrolumab (IFN- $\alpha$  receptor blocker), obinutuzumab (monoclonal anti-CD20), CFZ533X2202 (anti-CD40-CD40L), BMS-986165 (tyrosine kinase 2 inhibitor, blocks IL-12/23, interferon), and KZR-616 (targeted inhibition of immunoproteasome).

Combination therapy is the standard of care in LN and with the increased number of choices, making the right initial decision has become more complicated. The methodical approach that is generally followed in our practice is outlined in Figure 1. At present, it is not the standard of care to use a combination of biological agents, but biological medications in combination with other medicines with different mechanisms of action (MOA) are becoming commonplace [73].



**FIGURE 1: Treatment algorithm for lupus nephritis**

Treatment algorithm for LN

\*patient to be initiated on hydroxychloroquine, angiotensin-converting enzyme inhibitors or calcium channel blockers, statins, and adequate blood pressure control

Abbreviations: GC, glucocorticoids, MMF, mycophenolate mofeti

## Conclusions

Our review gives a comprehensive overview of the current understanding of LN and its treatment. It highlights the role of history, physical examination, and laboratory testing, as well as the importance of early diagnosis and treatment, the role of continuous monitoring of response to therapy, and the identification and treatment of complications of LN in reducing poor outcomes. It discusses the more recently approved therapies and outlines a treatment approach that makes use of various medications and their MOA. Despite the recent approval of two new drugs for LN, treatment is still difficult and is complicated by intolerance of medications, access, and, on occasion, compliance, given the large number of medications that may be needed.

As a result, despite the recent improvement in patient outcomes in SLE, renal involvement has a significant effect on the morbidity and mortality of patients, many of whom are women of color in the prime of

life. Lupus nephritis is one of the most severe manifestations of SLE that can still result in poorer outcomes, including ESRD and even death.

## Additional Information

### Disclosures

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

### Acknowledgements

The authors would like to thank Gita Verma, MD.

## References

- Font J, Cervera R, Ramos-Casals M, et al.: Clusters of clinical and immunologic features in systemic lupus erythematosus: analysis of 600 patients from a single center. *Semin Arthritis Rheum.* 2004, 33:217-30. [10.1053/S0049-0172\(03\)00133-1](https://doi.org/10.1053/S0049-0172(03)00133-1)
- Petri M, Orbai AM, Alarcón GS, et al.: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum.* 2012, 64:2677-86. [10.1002/art.34473](https://doi.org/10.1002/art.34473)
- Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W: The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. *Rheumatology (Oxford).* 2017, 56:1945-61. [10.1093/rheumatology/kex260](https://doi.org/10.1093/rheumatology/kex260)
- Stojan G, Petri M: Epidemiology of systemic lupus erythematosus: an update. *Curr Opin Rheumatol.* 2018, 30:144-50. [10.1097/BOR.0000000000000480](https://doi.org/10.1097/BOR.0000000000000480)
- Jorge AM, Lu N, Zhang Y, Rai SK, Choi HK: Unchanging premature mortality trends in systemic lupus erythematosus: a general population-based study (1999-2014). *Rheumatology (Oxford).* 2018, 57:337-44. [10.1093/rheumatology/kex412](https://doi.org/10.1093/rheumatology/kex412)
- Imran TF, Yick F, Verma S, et al.: Lupus nephritis: an update. *Clin Exp Nephrol.* 2016, 20:1-13. [10.1007/s10157-015-1179-y](https://doi.org/10.1007/s10157-015-1179-y)
- Lee YH, Choi SJ, Ji JD, Song GG: Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. *Lupus.* 2016, 25:727-34. [10.1177/0961203315627202](https://doi.org/10.1177/0961203315627202)
- Tektonidou MG, Dasgupta A, Ward MM: Risk of end-stage renal disease in patients with lupus nephritis, 1971-2015: a systematic review and Bayesian meta-analysis. *Arthritis Rheumatol.* 2016, 68:1432-41. [10.1002/art.39594](https://doi.org/10.1002/art.39594)
- Khanna R: Clinical presentation & management of glomerular diseases: hematuria, nephritic & nephrotic syndrome. *Mo Med.* 2011, 108:33-6.
- Sommer SC: Lupus nephritis. *Kidney Pathology Decennial 1966-1975.* Appleton-Century-Crofts, New York; 1975. 435-45.
- Appel G, Silva F, Pirani CL, Meltzer JI, Estes D: Renal involvement in systemic lupus erythematosus (SLE). A study of 56 patients emphasizing histologic classification. *Medicine.* 1978, 57:371-410.
- Weening JJ, D'Agati VD, Schwartz MM, et al.: The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int.* 2004, 65:521-30. [10.1111/j.1523-1755.2004.00443.x](https://doi.org/10.1111/j.1523-1755.2004.00443.x)
- Bajema IM, Wilhelmus S, Alpers CE, et al.: Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int.* 2018, 93:789-96. [10.1016/j.kint.2017.11.023](https://doi.org/10.1016/j.kint.2017.11.023)
- Kudose S, Santoriello D, Bomback AS, Stokes MB, D'Agati VD, Markowitz GS: Sensitivity and specificity of pathologic findings to diagnose lupus nephritis. *Clin J Am Soc Nephrol.* 2019, 14:1605-15. [10.2215/CJN.01570219](https://doi.org/10.2215/CJN.01570219)
- Mok CC: Understanding lupus nephritis: diagnosis, management, and treatment options. *Int J Womens Health.* 2012, 4:213-22. [10.2147/IJWH.S28034](https://doi.org/10.2147/IJWH.S28034)
- Alsuwaida A, Husain S, Alghonaim M, AlOudah N, Alwakeel J, Ullah A, Kfoury H: Strategy for second kidney biopsy in patients with lupus nephritis. *Nephrol Dial Transplant.* 2012, 27:1472-8. [10.1093/ndt/gfr517](https://doi.org/10.1093/ndt/gfr517)
- De Rosa M, Azzato F, Toblli JE, et al.: A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. *Kidney Int.* 2018, 94:788-94. [10.1016/j.kint.2018.05.021](https://doi.org/10.1016/j.kint.2018.05.021)
- Maningding E, Dall'Era M, Trupin L, Murphy LB, Yazdany J: Racial and ethnic differences in the prevalence and time to onset of manifestations of systemic lupus erythematosus: the California Lupus Surveillance Project. *Arthritis Care Res (Hoboken).* 2020, 72:622-9. [10.1002/acr.23887](https://doi.org/10.1002/acr.23887)
- Cross J, Jayne D: Diagnosis and treatment of kidney disease. *Best Pract Res Clin Rheumatol.* 2005, 19:785-98. [10.1016/j.berh.2005.05.005](https://doi.org/10.1016/j.berh.2005.05.005)
- Hull RP, Goldsmith DJ: Nephrotic syndrome in adults. *BMJ.* 2008, 336:1185-9. [10.1136/bmj.39576.709711.80](https://doi.org/10.1136/bmj.39576.709711.80)
- Sui M, Jia X, Yu C, et al.: Relationship between hypoalbuminemia, hyperlipidemia and renal severity in patients with lupus nephritis: a prospective study. *Cent Eur J Immunol.* 2014, 39:243-52. [10.5114/ceji.2014.43730](https://doi.org/10.5114/ceji.2014.43730)
- Hashmi MS, Pandey J: Nephritic Syndrome. *StatPearls [Internet]*, Treasure Island (FL); 2021.
- Vaziri ND: Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. *Kidney*

- Int. 2016, 90:41-52. [10.1016/j.kint.2016.02.026](https://doi.org/10.1016/j.kint.2016.02.026)
24. Agrawal S, Zaritsky JJ, Fornoni A, Smoyer WE: Dyslipidaemia in nephrotic syndrome: mechanisms and treatment. *Nat Rev Nephrol.* 2018, 14:57-70. [10.1038/nrneph.2017.155](https://doi.org/10.1038/nrneph.2017.155)
  25. Li SJ, Guo JZ, Zuo K, et al.: Thromboembolic complications in membranous nephropathy patients with nephrotic syndrome—a prospective study. *Thromb Res.* 2012, 130:501-5. [10.1016/j.thromres.2012.04.015](https://doi.org/10.1016/j.thromres.2012.04.015)
  26. Mintz G, Acevedo-Vázquez E, Gutiérrez-Espinosa G, Avelar-Garnica F: Renal vein thrombosis and inferior vena cava thrombosis in systemic lupus erythematosus. Frequency and risk factors. *Arthritis Rheum.* 1984, 27:539-44. [10.1002/art.1780270509](https://doi.org/10.1002/art.1780270509)
  27. Tektonidou MG, Sotsiou F, Nakopoulou L, Vlachoyiannopoulos PG, Moutsopoulos HM: Antiphospholipid syndrome nephropathy in patients with systemic lupus erythematosus and antiphospholipid antibodies: prevalence, clinical associations, and long-term outcome. *Arthritis Rheum.* 2004, 50:2569-79. [10.1002/art.20433](https://doi.org/10.1002/art.20433)
  28. Lai NS, Lan JL: Renal vein thrombosis in Chinese patients with systemic lupus erythematosus. *Ann Rheum Dis.* 1997, 56:562-4. [10.1136/ard.56.9.562](https://doi.org/10.1136/ard.56.9.562)
  29. Alvarez-Castells A, Sebastiá Cerqueda C, Quiroga Gómez S: Computerized tomography angiography of the renal vessels [Article in Spanish]. *Arch Esp Urol.* 2001, 54:603-15.
  30. Llach F: Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome. *Kidney Int.* 1985, 28:429-39. [10.1038/ki.1985.149](https://doi.org/10.1038/ki.1985.149)
  31. Appel GB, Williams GS, Meltzer JJ, Pirani CL: Renal vein thrombosis, nephrotic syndrome, and systemic lupus erythematosus: an association in four cases. *Ann Intern Med.* 1976, 85:310-7. [10.7326/0003-4819-85-3-310](https://doi.org/10.7326/0003-4819-85-3-310)
  32. Dall'Era M, Cisternas MG, Smilek DE, et al.: Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol.* 2015, 67:1305-13. [10.1002/art.39026](https://doi.org/10.1002/art.39026)
  33. Ugolini-Lopes MR, Seguro LP, Castro MX, Daffre D, Lopes AC, Borba EF, Bonfá E: Early proteinuria response: a valid real-life situation predictor of long-term lupus renal outcome in an ethnically diverse group with severe biopsy-proven nephritis?. *Lupus Sci Med.* 2017, 4:e000213. [10.1136/lupus-2017-000213](https://doi.org/10.1136/lupus-2017-000213)
  34. Enocsson H, Sjöwall C, Wirestam L, et al.: Four anti-dsDNA antibody assays in relation to systemic lupus erythematosus disease specificity and activity. *J Rheumatol.* 2015, 42:817-25. [10.3899/jrheum.140677](https://doi.org/10.3899/jrheum.140677)
  35. Walport M, Lachmann P: Complement deficiencies and abnormalities of the complement system in systemic lupus erythematosus and related disorders. *Curr Opin Rheumatol.* 1990, 2:661-5.
  36. Botto M, Dell'Agnola C, Bygrave AE, et al.: Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. *Nat Genet.* 1998, 19:56-9. [10.1038/ng0598-56](https://doi.org/10.1038/ng0598-56)
  37. Marto N, Bertolaccini ML, Calabuig E, Hughes GR, Khamashta MA: Anti-C1q antibodies in nephritis: correlation between titres and renal disease activity and positive predictive value in systemic lupus erythematosus. *Ann Rheum Dis.* 2005, 64:444-8. [10.1136/ard.2004.024943](https://doi.org/10.1136/ard.2004.024943)
  38. Yin Y, Wu X, Shan G, Zhang X: Diagnostic value of serum anti-C1q antibodies in patients with lupus nephritis: a meta-analysis. *Lupus.* 2012, 21:1088-97. [10.1177/0961203312451202](https://doi.org/10.1177/0961203312451202)
  39. Yang XW, Tan Y, Yu F, Zhao MH: Combination of anti-C1q and anti-dsDNA antibodies is associated with higher renal disease activity and predicts renal prognosis of patients with lupus nephritis. *Nephrol Dial Transplant.* 2012, 27:3552-9. [10.1093/ndt/gfs179](https://doi.org/10.1093/ndt/gfs179)
  40. Moroni G, Quaglioni S, Radice A, Trezzi B, Raffiotta F, Messa P, Sinico RA: The value of a panel of autoantibodies for predicting the activity of lupus nephritis at time of renal biopsy. *J Immunol Res.* 2015, 2015:106904. [10.1155/2015/106904](https://doi.org/10.1155/2015/106904)
  41. Parodis I, Arnaud L, Gerhardsson J, et al.: Antiphospholipid antibodies in lupus nephritis. *PLoS One.* 2016, 11:e0158076. [10.1371/journal.pone.0158076](https://doi.org/10.1371/journal.pone.0158076)
  42. Beck LH Jr, Bonegio RG, Lambeau G, et al.: M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med.* 2009, 361:11-21. [10.1056/NEJMoa0810457](https://doi.org/10.1056/NEJMoa0810457)
  43. Hahn BH, McMahon MA, Wilkinson A, et al.: American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken).* 2012, 64:797-808. [10.1002/acr.21664](https://doi.org/10.1002/acr.21664)
  44. Rhen T, Cidlowski JA: Antiinflammatory action of glucocorticoids — new mechanisms for old drugs. *N Engl J Med.* 2005, 353:1711-23. [10.1056/NEJMra050541](https://doi.org/10.1056/NEJMra050541)
  45. Stahn C, Buttgerit F: Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol.* 2008, 4:525-33. [10.1038/ncprheum0898](https://doi.org/10.1038/ncprheum0898)
  46. Strehl C, Buttgerit F: Unraveling the functions of the membrane-bound glucocorticoid receptors: first clues on origin and functional activity. *Ann N Y Acad Sci.* 2014, 1318:1-6. [10.1111/nyas.12364](https://doi.org/10.1111/nyas.12364)
  47. Wilhelmus S, Bajema IM, Bertsias GK, et al.: Lupus nephritis management guidelines compared. *Nephrol Dial Transplant.* 2016, 31:904-13. [10.1093/ndt/gfv102](https://doi.org/10.1093/ndt/gfv102)
  48. Fanouriakis A, Kostopoulou M, Cheema K, et al.: 2019 update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis.* 2020, 79:713-23. [10.1136/annrheumdis-2020-21692](https://doi.org/10.1136/annrheumdis-2020-21692)
  49. Pons-Estel GJ, Alarcón GS, McGwin G Jr, et al.: Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXX, data from a multiethnic US cohort. *Arthritis Rheum.* 2009, 61:830-9. [10.1002/art.24538](https://doi.org/10.1002/art.24538)
  50. Tselios K, Koumaras C, Urowitz MB, Gladman DD: Do current arterial hypertension treatment guidelines apply to systemic lupus erythematosus patients? A critical appraisal. *Semin Arthritis Rheum.* 2014, 43:521-5. [10.1016/j.semarthrit.2013.07.007](https://doi.org/10.1016/j.semarthrit.2013.07.007)
  51. Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A: Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int.* 2004, 65:1991-2002. [10.1111/j.1523-1755.2004.00620.x](https://doi.org/10.1111/j.1523-1755.2004.00620.x)
  52. Abud-Mendoza C, de la Fuente H, Cuevas-Orta E, Baranda L, Cruz-Rizo J, González-Amaro R: Therapy with statins in patients with refractory rheumatic diseases: a preliminary study. *Lupus.* 2003, 12:607-11.

- [10.1191/0961203503lu429oa](https://doi.org/10.1191/0961203503lu429oa)
53. Lawman S, Mauri C, Jury EC, Cook HT, Ehrenstein MR: Atorvastatin inhibits autoreactive B cell activation and delays lupus development in New Zealand black/white F1 mice. *J Immunol.* 2004, 173:7641-6. [10.4049/jimmunol.173.12.7641](https://doi.org/10.4049/jimmunol.173.12.7641)
  54. van Leuven SI, Mendez-Fernandez YV, Stroes ES, Tak PP, Major AS: Statin therapy in lupus-mediated atherogenesis: two birds with one stone?. *Ann Rheum Dis.* 2011, 70:245-8. [10.1136/ard.2010.133827](https://doi.org/10.1136/ard.2010.133827)
  55. Barron KS, Person DA, Brewer EJ Jr, Beale MG, Robson AM: Pulse methylprednisolone therapy in diffuse proliferative lupus nephritis. *J Pediatr.* 1982, 101:137-41. [10.1016/S0022-3476\(82\)80203-5](https://doi.org/10.1016/S0022-3476(82)80203-5)
  56. Mejía-Vilet JM, Ayoub I: The use of glucocorticoids in lupus nephritis: new pathways for an old drug . *Front Med (Lausanne).* 2021, 8:622225. [10.3389/fmed.2021.622225](https://doi.org/10.3389/fmed.2021.622225)
  57. Lightstone L, Doria A, Wilson H, Ward FL, Larosa M, Bargman JM: Can we manage lupus nephritis without chronic corticosteroids administration?. *Autoimmun Rev.* 2018, 17:4-10. [10.1016/j.autrev.2017.11.002](https://doi.org/10.1016/j.autrev.2017.11.002)
  58. Steinberg AD, Steinberg SC: Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. *Arthritis Rheum.* 1991, 34:945-50. [10.1002/art.1780340805](https://doi.org/10.1002/art.1780340805)
  59. Ginzler EM, Dooley MA, Aranow C, et al.: Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med.* 2005, 353:2219-28. [10.1056/NEJMoa043731](https://doi.org/10.1056/NEJMoa043731)
  60. Walsh M, James M, Jayne D, Tonelli M, Manns BJ, Hemmelgarn BR: Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2007, 2:968-75. [10.2215/CJN.01200307](https://doi.org/10.2215/CJN.01200307)
  61. Isenberg D, Appel GB, Contreras G, et al.: Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. *Rheumatology (Oxford).* 2010, 49:128-40. [10.1093/rheumatology/kep346](https://doi.org/10.1093/rheumatology/kep346)
  62. Chan TM, Li FK, Tang CS, et al.: Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med.* 2000, 343:1156-62. [10.1056/NEJM200010193431604](https://doi.org/10.1056/NEJM200010193431604)
  63. Schweitzer E, Yoon S, Fink J, et al.: Mycophenolate mofetil reduces the risk of acute rejection less in African-American than in Caucasian kidney recipients. *Transplantation.* 1998, 27:242-8.
  64. Houssiau FA, Vasconcelos C, D'Cruz D, et al.: The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis.* 2010, 69:61-4. [10.1136/ard.2008.102533](https://doi.org/10.1136/ard.2008.102533)
  65. Mok CC, Ying KY, Yim CW, Siu YP, Tong KH, To CH, Ng WL: Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. *Ann Rheum Dis.* 2016, 75:30-6. [10.1136/annrheumdis-2014-206456](https://doi.org/10.1136/annrheumdis-2014-206456)
  66. Lanata CM, Mahmood T, Fine DM, Petri M: Combination therapy of mycophenolate mofetil and tacrolimus in lupus nephritis. *Lupus.* 2010, 19:935-40. [10.1177/0961203310365714](https://doi.org/10.1177/0961203310365714)
  67. Laskow DA, Vincenti F, Neylan JF, Mendez R, Matas AJ: An open-label, concentration-ranging trial of FK506 in primary kidney transplantation. A report of the United States Multicenter FK506 Kidney Transplant Group. *Transplantation.* 1996, 62:900-905.
  68. Rovin BH, Teng YKO, Ginzler EM, et al.: Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2021, 29:2070-80. [10.1016/S0140-6736\(21\)00578-X](https://doi.org/10.1016/S0140-6736(21)00578-X)
  69. Dooley MA, Jayne D, Ginzler EM, et al.: Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med.* 2011, 365:1886-95. [10.1056/NEJMoa1014460](https://doi.org/10.1056/NEJMoa1014460)
  70. Kim M, Rostas S, Gabardi S: Mycophenolate fetal toxicity and risk evaluation and mitigation strategies . *Am J Transplant.* 2013, 13:1383-9. [10.1111/ajt.12238](https://doi.org/10.1111/ajt.12238)
  71. Fischer-Betz R, Specker C, Brinks R, Aringer M, Schneider M: Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. *Rheumatology (Oxford).* 2013, 52:1070-6. [10.1093/rheumatology/kes425](https://doi.org/10.1093/rheumatology/kes425)
  72. Furie R, Rovin BH, Houssiau F, et al.: Two-year, randomized controlled trial of belimumab in lupus nephritis. *N Engl J Med.* 2020, 383:1117-28. [10.1056/NEJMoa2001180](https://doi.org/10.1056/NEJMoa2001180)
  73. An Y, Zhang H, Liu Z: Individualizing therapy in lupus nephritis . *Kidney Int Rep.* 2019, 4:1366-72. [10.1016/j.ekir.2019.08.005](https://doi.org/10.1016/j.ekir.2019.08.005)