# KDOQI US Commentary on the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis

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The Kidney Disease Outcomes Quality Initiative (KDOQI) convened a work group to review the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis (LN). The management of LN has become increasingly individualized, and treatment options are expanding; for example, since the release of the KDIGO guideline, the US Food and Drug Administration has approved obinutuzumab in addition to belimumab and voclosporin for the treatment of LN, and the enrollment of patients in chimeric antigen receptor (CAR) T-cell therapy clinical trials is changing the treatment landscape for autoimmune diseases including systemic lupus erythematosus. The use of combination therapy and the trend toward lower doses of corticosteroids for LN management are also part of this transformation. The KDOQI work group reviewed the KDIGO guideline statements and practice points and provides perspectives for implementation within the context of clinical practice in the United States. This commentary is the product of the KDOQI work group and presents the recommendations and practice points from the KDIGO guideline, followed by commentary and brief notes on clinical utility, implementation, and challenges.

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## Introduction

Lupus nephritis (LN) is associated with significant morbidity and mortality in patients with systemic lupus erythematosus (SLE). The 2024 KDIGO guideline discusses the importance of early kidney biopsy for the diagnosis of severe LN, whose poor prognosis can only be altered with early and appropriate immunosuppressive therapy.[1] The guideline also provides a comprehensive approach for the general management of patients with LN who commonly have other organ involvement and complications beyond kidney disease. General management of people with SLE and LN includes collaboration with rheumatologists.

For the management of LN with immunosuppression, clinical trials completed over the last 18 years have demonstrated significantly higher remission with triple immunosuppressive regimens for induction treatment of active and severe LN without excessive risk of serious adverse events (SAEs) compared with double immunosuppressive regimens. Therefore, an important change in the KDIGO 2024 guideline compared with the 2021 guideline is the recommendation of triple immunosuppressive therapies as the first-line therapy for active and severe classes III/IV LN. Currently, there are several available triple immunosuppressive therapy regimens. Because no studies have directly compared the efficacy and safety of different triple therapy induction regimens, decisions about immunosuppression require discussion between patients and providers. The KDIGO 2024 guideline also provides recommendations about long-term maintenance therapy, with mycophenolic acid analogs as the first choice to prevent relapse, one of the most important causes of progressive chronic kidney disease (CKD). The KDOQI work group believes that determining the best time to discontinue long-term immunosuppression remains a major area of uncertainty given the mixed results from the few clinical trials of maintenance therapy withdrawal to assess the risk of relapse.

Approximately 10% of patients with LN develop end-stage kidney disease (ESKD) due to the lack of sustained remission. In this commentary, the KDOQI work group notes that patients with LN and ESKD are less likely to be transplanted, and most are treated with dialysis; further, fewer than 5% of LN patients in the United States who are approaching ESKD receive preemptive kidney transplantation, which is the preferred kidney replacement therapy (KRT).

## Review and Approval Process for This Commentary

The KDOQI Steering Committee selected members of the KDOQI work group based on their clinical and research expertise as well as their interest in the guideline process and experience taking care of people with LN. KDOQI work group members reviewed recent literature and provided commentary on the KDIGO guideline recommendations. The work group discussed the guideline via teleconference, and all work group members and KDOQI

leadership reviewed and approved the commentary. This review and commentary follow the same order and numbering scheme used in the KDIGO guideline. All KDIGO guideline practice points and recommendations are reproduced, although commentary is not provided for each. The KDOQI work group agrees with the practice points and recommendations for which they have provided no commentary. For the guideline recommendations that may have implications for clinical care in the United States, we present comments and discuss their clinical utility and implementation. All material is reproduced with permission of KDIGO.

## 10.1. Diagnosis

Practice Point 10.1.1: Approach to the diagnosis of kidney involvement in systemic lupus erythematosus (SLE) (Figure 1)

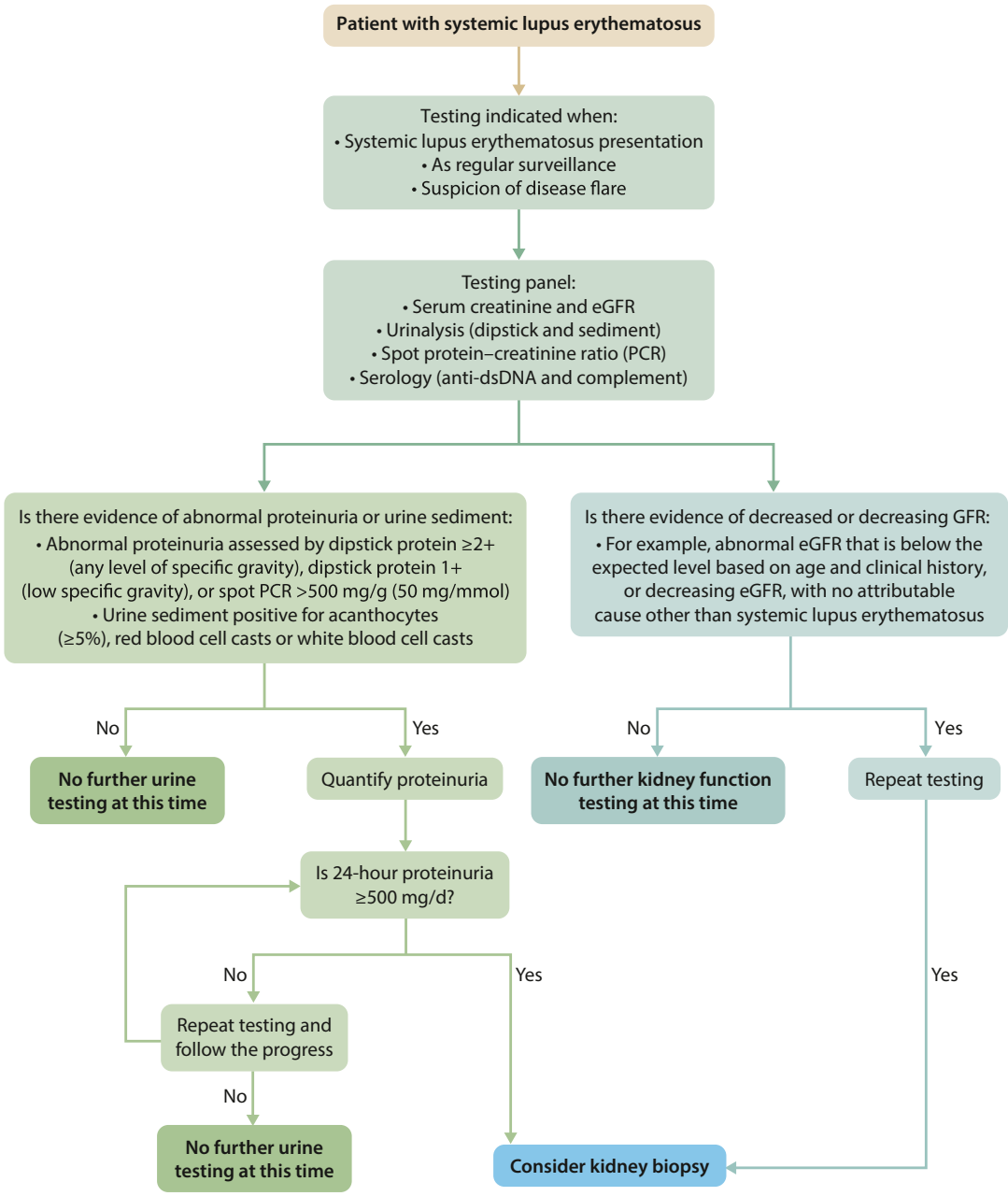


**Figure 1.** Diagnosis of kidney involvement in systemic lupus erythematosus. Abbreviations: anti-dsDNA, anti-double-stranded DNA; eGFR, estimated glomerular filtration rate; PCR, protein-creatinine ratio.

### Commentary and Clinical Utility

Lupus nephritis (LN) often develops concurrently or shortly following the onset of SLE, particularly in high-risk non-White populations. Appropriately, Figure 1 of the KDIGO guideline recommends screening for LN in people with SLE at the time of the disease onset, during follow-up visits, and at flare events, recommending the following tests: serum creatinine with estimated glomerular filtration rate (eGFR), complete urinalysis, spot or random urinary protein-creatinine ratio (UPCR), complement components, and anti-double-stranded DNA (anti-dsDNA) levels. The KDOQI work group agrees with the screening list of renal function tests but recommends expanding the serology tests to include the antinuclear antibody (ANA) comprehensive panel with many more autoantibodies targeting pathogenic antigens. The available anti-dsDNA tests have only moderate sensitivity in diagnosing LN, between 66.7% and 79.5%, with false negative rates between 20.5% and 25.3%.[2]

SLE is a heterogeneous immune complex disease, meaning that the targeted antigens of clinical manifestations such as LN can vary widely in affected patients. Figure 1 also appropriately recommends a confirmatory 24-hour urine analysis for quantification of proteinuria, standardized by creatinine excretion. Practice Point 10.1.1 recommended a kidney biopsy with the proteinuria threshold of >500 mg/day or UPCR > 500 mg/g, or positive urine sediment for acanthocytes, casts of red blood cells or white blood cells, or worsening serum creatinine or eGFR.

We highlight also the importance of sterile pyuria, seen with an underlying active hypercellular glomerulonephritis and/or active interstitial nephritis. Patients with LN and sterile pyuria are frequently misdiagnosed with urinary tract infections by providers without experience in recognizing the signs of active LN. Importantly, Practice Point 10.1.1 highlights that active glomerulonephritis can be found during kidney biopsies, with lower-level proteinuria or minimal changes in the urine sediment or serum creatinine; in that context, clinicians must balance the benefit and risk of recommending an earlier kidney biopsy. The kidney biopsy is very important to categorize LN, assess the activity and chronicity indices, and exclude a coexisting pathology with or without relatedness to SLE. Good outcomes can be expected with early recognition and treatment of LN, particularly of classes III, IV, and V.

### Implementation and Challenges

Regarding the regularity of renal function and serology tests during follow-up visits in patients with LN, the KDIGO guideline avoids providing frequency for clinical tests. The 2024 American College of Rheumatology (ACR) Guideline for the Screening, Treatment, and Management of Lupus Nephritis[3] recommends tests every 6 months after achieving control of relapse events and every 12 months in patients with long-standing inactive disease. The ideal frequency of clinical tests during follow-up remains unclear, in part due to the lack of comprehensive studies primarily focusing on testing frequency for the diagnosis of LN relapses and consequences such as progressive CKD and mortality. However, we recommend monthly clinical tests during the induction treatment of active LN and quarterly testing during maintenance therapy, particularly in high-risk populations. Early diagnosis and treatment of new or relapsing LN, particularly severe LN, is critically important to avoid poor outcomes.

## 10.2. Treatment

### 10.2.1. General Management of Patients With Lupus Nephritis

**Recommendation 10.2.1.1: We recommend that patients with SLE, including those with lupus nephritis (LN), be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated (*1C*).**

Practice Point 10.2.1.1: Adjunctive therapies to manage LN and attenuate complications of the disease or its treatments should be considered for all patients, as outlined in Figure 2 [Fig 3 in the KDIGO Guideline].

#### *Commentary and Clinical Utility*

The work group agrees with the recommendations of general management of patients with LN, as illustrated in Figure 2 (Fig 3 in the KDIGO guideline). The general management of patients with LN should not differ from that of SLE patients without LN. We also agree that patients with LN should be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated. Patients treated with these medications have a lower risk of flares but must have an annual eye examination to screen for toxicity. General management as well as the management of LN should be in collaboration with rheumatologist colleagues with the goal of minimizing the risk of complications.

### 10.2.2. Class I or Class II Lupus Nephritis

Practice Point 10.2.2.1: Approach to immunosuppressive treatment for patients with Class I or Class II LN (Figure 3 [Fig 4 in the KDIGO Guideline])

#### *Commentary and Clinical Utility*

The KDOQI work group agrees with Practice Point 10.2.2.1, and Figure 3 (Fig 4 in the KDIGO guideline) highlights that patients with classes I and II LN usually present with mild proteinuria and/or microscopic hematuria with normal eGFR, without needing specific immunosuppressive therapy beyond what is used to control extrarenal SLE activity. Also, patients with class I/II LN can

| Risk | Risk attenuation |
|---|---|
| **Cardiovascular risk** | • Lifestyle modifications – smoking cessation, body weight optimization, exercise<br>• Dyslipidemia management<br>• Low-dose aspirin during pregnancy<br>• Blood pressure control |
| **Proteinuria and CKD progression (refer to Chapter 1)** | • Avoid high-sodium diet<br>• Optimize blood pressure<br>• Renoprotective medications, such as RAAS blockade, SGLT2 inhibitor, etc., in stable patients without AKI<br>• Avoid nephrotoxic insult<br>• Prevent AKI |
| **Infection risk** | • Assess medical history of herpes zoster and tuberculosis<br>• Screening for HBV, HCV, HIV, and HBV vaccination<br>• *Pneumocystis jirovecii* prophylaxis (issue of potential adverse drug reaction discussed below)<br>• Influenza and pneumococcal vaccination<br>• Individualized consideration for recombinant zoster vaccine<br>• Individualized consideration for other infectious organisms as dictated by public health concerns at the time of treatment |
| **Bone injury** | • Bone mineral density and fracture risk assessment<br>• Calcium and vitamin D supplementation<br>• Bisphosphonates when appropriate |
| **Ultraviolet light exposure** | • Broad-spectrum sunscreen<br>• Limit ultraviolet light exposure |
| **Premature ovarian failure** | • Gonadotropin-releasing hormone agonists (i.e. leuprolide)<br>• Sperm/oocyte cryopreservation |
| **Unplanned pregnancy** | • Individual evaluation and counselling for contraception type (preference, thrombosis risk, age) |
| **Cancer** | • Evaluate individual risk factors for malignancies<br>• Age-specific malignancy screening<br>• Minimize lifetime cyclophosphamide exposure to <36 g |

**Figure 2.** Measures to minimize the risk of complications related to lupus nephritis or its treatment. (Note: Chapter 1 refers to chapter 1 of the KDIGO Guideline on Glomerular Diseases.) Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium/glucose cotransporter 2.

occasionally present with corticosteroid-responsive nephrotic syndrome due to an underlying podocytopathy. The light microscopic examination is normal in class I LN. The light microscopic examination exhibits mesangial hypercellularity in class II LN. Both classes I and II LN are characterized by immune complex deposition in the mesangium, seen in the direct immunofluorescence and electron microscopic examinations of biopsies.

### *Implementation and Challenges*

Although classes I and II LN are considered benign, the follow-up of these patients can be challenging because of the high risk of histological transformation to a severe class of LN over the long term. Importantly, 34% to 63% of patients with class II LN can transform to classes III, IV, and V; therefore, regularly testing kidney function, ANA comprehensive panel, and complement component levels are important in high-risk populations with class II LN, with the recommendation that the kidney biopsy is repeated when clinical tests show worsening kidney function. Notably, patients with class II LN can occasionally reveal minimal subendothelial or/and subepithelial deposits in their first biopsies, suggesting a high risk of transformation to severe LN. Longitudinal studies

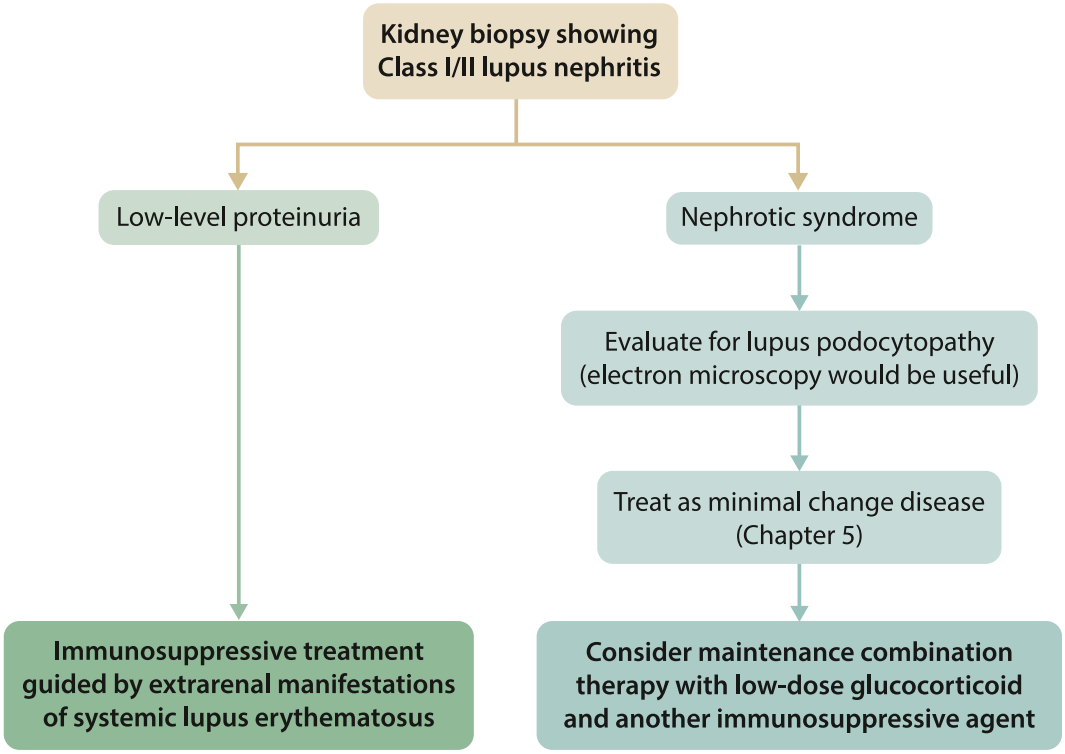


**Figure 3.** Immunosuppressive treatment for patients with class I or class II lupus nephritis. (Note: Chapter 5 refers to Chapter 5 of the KDIGO Guideline on Glomerular Diseases.)

particularly focusing on this subgroup of patients with class II LN and minimal subendothelial or/and subepithelial deposits are lacking.

## 10.2.3. Class III or Class IV Lupus Nephritis

### *10.2.3.1. Initial Therapy of Active Class III/IV Lupus Nephritis*

**Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus any one of the following:**

i **mycophenolic acid analogs (MPAA) (*1B*); or**
ii **low-dose intravenous cyclophosphamide (*1B*); or**
iii **belimumab and either MPAA or low-dose intravenous cyclophosphamide (*1B*); or**
iv **MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (i.e., estimated glomerular filtration rate [eGFR] ≤45 ml/min per 1.73 m²) (*1B*)**

Practice Point 10.2.3.1.1: A regimen of reduced-dose glucocorticoids following a short course of methylprednisolone pulses may be considered during the initial treatment of active LN when both the kidney and extrarenal disease manifestations show satisfactory improvement (Figure 4 [Fig 7 in the KDIGO guideline]).

Practice Point 10.2.3.1.2: Intravenous cyclophosphamide can be used as the initial therapy for active Class III and Class IV LN in patients who may have difficulty adhering to an oral regimen.

Practice Point 10.2.3.1.3: An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at high risk of infertility, such as patients who have a moderate-to-high prior cyclophosphamide exposure.

Practice Point 10.2.3.1.4: Initial therapy with an immunosuppressive regimen that includes a CNI (voclosporin, tacrolimus, or cyclosporine) may be preferred in patients with relatively preserved kidney function and nephrotic range proteinuria likely due to extensive podocyte injury, as well as patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.

Practice Point 10.2.3.1.5: A triple immunosuppressive regimen of belimumab with glucocorticoids and either MPAA or reduced-dose cyclophosphamide may be preferred in patients with repeated kidney flares or at high-risk for progression to kidney failure due to severe chronic kidney disease.

Practice Point 10.2.3.1.6: Other therapies, such as azathioprine or leflunomide combined with glucocorticoids, may be considered in lieu of the recommended initial drugs for proliferative LN in situations of patient intolerance, lack of availability, and/or excessive cost of standard drugs, but these alternatives may be associated with inferior efficacy, including increased rate of disease flares and/or increased incidence of drug toxicities.

Practice Point 10.2.3.1.7: Newer biologic and non-biologic therapies are under development and may offer future options for the treatment of active LN. Rituximab may be considered for patients with persistent disease activity or inadequate response to initial standard-of-care therapy.

***Commentary and Clinical Utility.*** For the induction treatment of active and severe Class III or IV LN, with or without a membranous component, the use of triple immunosuppressive regimens as a first-line treatment has demonstrated significantly higher remission of LN without an excessive risk of SAEs compared with double immunosuppressive regimens. Clinical trials of triple immunosuppressive regimens, combining a calcineurin inhibitor (CNI: voclosporin or tacrolimus) or the B-lymphocyte stimulator inhibitor belimumab or the anti-CD20 monoclonal obinutuzumab with the double immunosuppressive regimen (mycophenolate or sequential cyclophosphamide followed by azathioprine and corticosteroids) were successfully completed, resulting in the approval by the US Food and Drug Administration (FDA) of obinutuzumab in addition to 2 other agents, belimumab and voclosporin. Compared with patients treated with the double immunosuppressive therapy alone, significantly more patients treated with triple immunosuppressive therapies of tacrolimus plus mycophenolate and corticosteroids (25.6% vs 45.9%, $P < 0.001$),[4] voclosporin plus mycophenolate and corticosteroids (23% vs 41%, $P < 0.0001$),[5] belimumab plus mycophenolate or sequential cyclophosphamide followed by azathioprine and corticosteroids (20% vs 30%, $P = 0.02$),[6] and obinutuzumab plus mycophenolate and corticosteroids (33.1% vs 46.4%, $P = 0.02$)[7] achieved complete renal remission (Table 1). Compared with patients who received double immunosuppressive therapy, the patients who received any of the triple immunosuppressive therapy regimens did not have excessive risk of SAEs or infectious events (Table 1).

The KDOQI work group agrees with Practice Point 10.2.3.1.1 to use reduced-dose glucocorticoids to manage active class III/IV LN. Figure 4 (Fig 7 in the KDIGO guideline) notes a broad range for intravenous methylprednisolone: 250-1,000 mg per day commonly prescribed as 500 mg daily for 3 days, with tapering dictated by clinical context. Under the reduced-dose steroid regimen, the aim is to completely taper prednisone to <5 mg daily by weeks 21 to 24. The ACR supports a maximum oral prednisone dose of 40 mg daily and conditionally endorses pulse glucocorticoids (250-1,000 mg for 1-3 days). KDIGO emphasizes the anti-inflammatory role of steroids and the lag in effects of other immunosuppressants while acknowledging that practices vary among nephrologists. The ACR also recognizes that recent trials have used lower steroid doses and highlights that patient preferences and steroid-related side effects support minimization of steroids when feasible.

The KDIGO and ACR guidelines concur that tapering regimens should be individualized based on renal and extrarenal manifestations. Notably, the role of intravenous methylprednisolone is not clearly stated in previous studies; generally, it is acceptable to include intravenous methylprednisolone as the initial treatment in patients with rapidly progressive glomerulonephritis, which is usually associated with a high degree of proteinuria, rapid kidney function decline, crescents and/or fibrinoid necrosis on biopsy, and severe extrarenal symptoms such as central nervous system involvement. It is important to note that the suggested steroid dose refers to treatment of active LN, and the activity score is determined based on biopsy findings. The activity index comprises endocapillary hypercellularity, the presence of neutrophils and/or karyorrhexis, fibrinoid necrosis, hyalin deposits, cellular or

| | High-dose scheme | Moderate-dose scheme | Reduced-dose scheme |
|---|---|---|---|
| **Methylprednisolone intravenous pulses** | Nil or 0.25–0.5 g/day up to 3 days as initial treatment | 0.25–0.5 g/day up to 3 days often included as initial treatment | 0.25–0.5 g/day up to 3 days usually included as initial treatment |
| **Oral prednisone equivalent (/day)** | | | |
| Week 0–2 | 0.8–1.0 mg/kg (max 80 mg) | 0.6–0.7 mg/kg (max 50 mg) | 0.5–0.6 mg/kg (max 40 mg) |
| Week 3–4 | 0.6–0.7 mg/kg | 0.5–0.6 mg/kg | 0.3–0.4 mg/kg |
| Week 5–6 | 30 mg | 20 mg | 15 mg |
| Week 7–8 | 25 mg | 15 mg | 10 mg |
| Week 9–10 | 20 mg | 12.5 mg | 7.5 mg |
| Week 11–12 | 15 mg | 10 mg | 5 mg |
| Week 13–14 | 12.5 mg | 7.5 mg | 2.5 mg |
| Week 15–16 | 10 mg | 7.5 mg | 2.5 mg |
| Week 17–18 | 7.5 mg | 5 mg | 2.5 mg |
| Week 19–20 | 7.5 mg | 5 mg | 2.5 mg |
| Week 21–24 | 5 mg | <5 mg | 2.5 mg |
| Week >25 | <5 mg | <5 mg | <2.5 mg |

**Figure 4.** Examples of glucocorticoid regimens for lupus nephritis. Abbreviations: max, maximum.

**Table 1.** Frequencies of efficacy and safety outcomes according to therapy groups with definitions of primary renal response and complete renal remission in selected randomized controlled trials for induction of lupus nephritis

| Randomized Controlled Trials | Summary of Therapy Groups | Patients With PRR Events | Patients With CRR Events | Total Patients in Efficacy | Patients With SAE Events | Patients With SIE Events | Total Patients in Safety | Definition of Primary Efficacy Outcome PRR | Definition of Secondary Efficacy Outcome CRR |
|---|---|---|---|---|---|---|---|---|---|
| MTT 2015[4] | IV cyclophosphamide + corticosteroids | — | 46 | 181 | 5 | 4 | 181 | Same as CRR | Proteinuria < 0.4 g/d, serum albumin ≥35 g/L, normal stable creatinine, and inactive sediment at 24 weeks. |
| | Triple: MMF + tacrolimus + corticosteroids | — | 83 | 181 | 13 | 11 | 181 | | |
| BLISS-LN 2020[6] | MMF + corticosteroids or Euro-Lupus cyclophosphamide + corticosteroids | 72 | 44 | 223 | 67 | 31 | 224 | UPCR ≤0.7 g/g, eGFR ≥ 60 and ≤20% within baseline, no use of rescue therapy, and ≤10 mg/day of prednisone from week 76 to week 104. | UPCR < 0.5 g/g, eGFR ≥ 90 and ≤15% within baseline, no use of rescue therapy, and ≤10 mg/day of prednisone from week 76 to week 104. |
| | Triple: MMF + belimumab + corticosteroids or Euro-Lupus cyclophosphamide + belimumab + corticosteroids | 96 | 67 | 223 | 58 | 30 | 224 | | |
| AURORA 2021[5] | MMF + corticosteroids | — | 40 | 178 | 38 | 20 | 178 | Same as CRR | UPCR ≤0.5 g/g, eGFR > 60 and ≤20% within baseline, no use of rescue therapy, and ≤10 mg/day of prednisone for 3 consecutive days or for more than 7 total days from week 44 to week 52. |
| | Triple: MMF + voclosporin + corticosteroids | — | 73 | 179 | 37 | 18 | 178 | | |
| REGENCY 2025[7] | MMF + corticosteroids | — | 45 | 136 | 24 | 10 | 132 | Same as CRR | UPCR <0.5 g/g, ≥85% eGFR of baseline, no use of rescue therapy, and ≤7.5 mg/day of prednisone from week 64 to week 76. |
| | Triple: MMF + obinutuzumab + corticosteroids | — | 63 | 135 | 44 | 23 | 136 | | |

In the United States, the US Food and Drug Administration (FDA) has approved belimumab for the treatment of patients with active systemic lupus erythematosus and severe active lupus nephritis; voclosporin and obinutuzumab are approved by the FDA for the treatment of patients with severe and active lupus nephritis; and tacrolimus is approved by the FDA for the treatment of rejection prophylaxis in patients with solid organ transplants. Tacrolimus is used off FDA label for the treatment of patients with severe and active lupus nephritis. Tacrolimus is approved by other regulatory agencies in Japan and other Asian countries for the treatment of patients with severe and active lupus nephritis.
Abbreviations: CRR, complete renal remission; eGFR, estimated glomerular filtration rate. MMF, mycophenolate mofetil; PRR, primary renal response; SAE, serious adverse event; SIE, severe infection event; UPCR, urinary protein-creatinine ratio.

| Components of the activity index | Score | Calculating the activity score<br>Extent of lesion | Points |
|---|---|---|---|
| • Endocapillary hypercellularity<br>• Neutrophils and/or karyorrhexis<br>• Fibrinoid necrosis<br>• Hyaline deposits (wire loop and/or hyaline thrombi)<br>• Cellular/fibrocellular crescents<br>• Interstitial inflammation (interstitial leukocytes) | 0–3<br>0–3<br>(0–3) × 2<br>0–3<br>(0–3) × 2<br>0–3<br>**Total: 0–24** | Not present<br>Present in <25%<br>Present in 25%–50%<br>Present in >50% | 0<br>1<br>2<br>3 |
| **Items included in the NIH chronicity score** | **Score** | **Calculating the chronicity score**<br>**Extent of lesion** | **Points** |
| • Total glomerulosclerosis (global + segmental)<br>• Fibrous crescents<br>• Interstitial fibrosis<br>• Tubular atrophy | 0–3<br>0–3<br>0–3<br>0–3<br>**Total: 0–12** | Present in <10%<br>Present in 10%–25%<br>Present in 25%–50%<br>Present in >50% | 0<br>1<br>2<br>3 |
| **Other histologic findings not included in the activity or chronicity score** | | | |
| • Foot process effacement (lupus podocytopathy)<br>• Collapsing lupus glomerulopathy<br>• Vascular lesions (arteriosclerosis, non-inflammatory vascular immune complex deposits, thrombotic microangiopathy, non-inflammatory necrotizing vasculitis, true renal vasculitis) | | | |

**Figure 5.** Activity and chronicity items included in lupus nephritis kidney biopsy report. NIH, National Institutes of Health.

fibrocellular crescents, and interstitial inflammation. The activity score is calculated based on the extent and severity of these lesions (Fig 5 [Fig 2 in the KDIGO guideline]).

For patients with chronic class III or IV LN, with or without class V, the KDIGO guideline recommends supportive care for CKD. If class V is present, the patient should be managed according to the class V LN guideline (see also Practice Point 10.2.4). The data on the optimal steroid dose for class V LN are controversial; however, it is suggested to use low to medium doses (Fig 6 [Fig 5 in the KDIGO guideline]).

Cyclophosphamide has traditionally been used for treatment of LN; however, with the emerging therapeutic options it is becoming less common as a first-line therapy, especially in female patients of childbearing age. We agree with Practice Point 10.2.3.1.3; a mycophenolic acid analog (MPAA)–based regimen is preferable in patients who wish to become pregnant in the future. This consideration is crucial because lupus is more common in younger women of childbearing age, and fertility preservation should be part of a thorough patient-centered discussion before initiating therapy. The 2 well-studied cyclophosphamide regimens are the National Institutes of Health (NIH) and the Euro-Lupus regimens (Fig 7 [Fig 6 in the KDIGO guideline]). The NIH regimen was studied in people from multiple ethnicities and provides broader generalizability whereas the Euro-Lupus data are limited to mainly White patients. The Euro-Lupus regimen recommends cyclophosphamide at 500 mg every 2 weeks for 3 months whereas a high-dose NIH regimen suggests 500-1,000 mg per $m^2$ of body surface area every month for a total of 6 months. Navigating how to adhere to an infusion regimen for 6 months might be challenging for younger patients.

We agree with the preference for CNIs in patients with preserved kidney function and nephrotic range proteinuria, in line with Practice Point 10.2.3.1.4. However, we note that data are lacking regarding the long-term efficacy of CNIs in long-term kidney function preservation. KDIGO suggests adding belimumab to MPAA or reduced-dose cyclophosphamide and steroids in patients at high risk for progression to kidney failure due to severe CKD. In addition, patients with a baseline eGFR of <45 mL/min/1.73 $m^2$ were excluded from the AURORA trial, and KDIGO emphasizes the insufficient data on the use of voclosporin in pregnancy.

***Implementation and Challenges.*** A combination regimen of immunosuppressive agents and low-dose

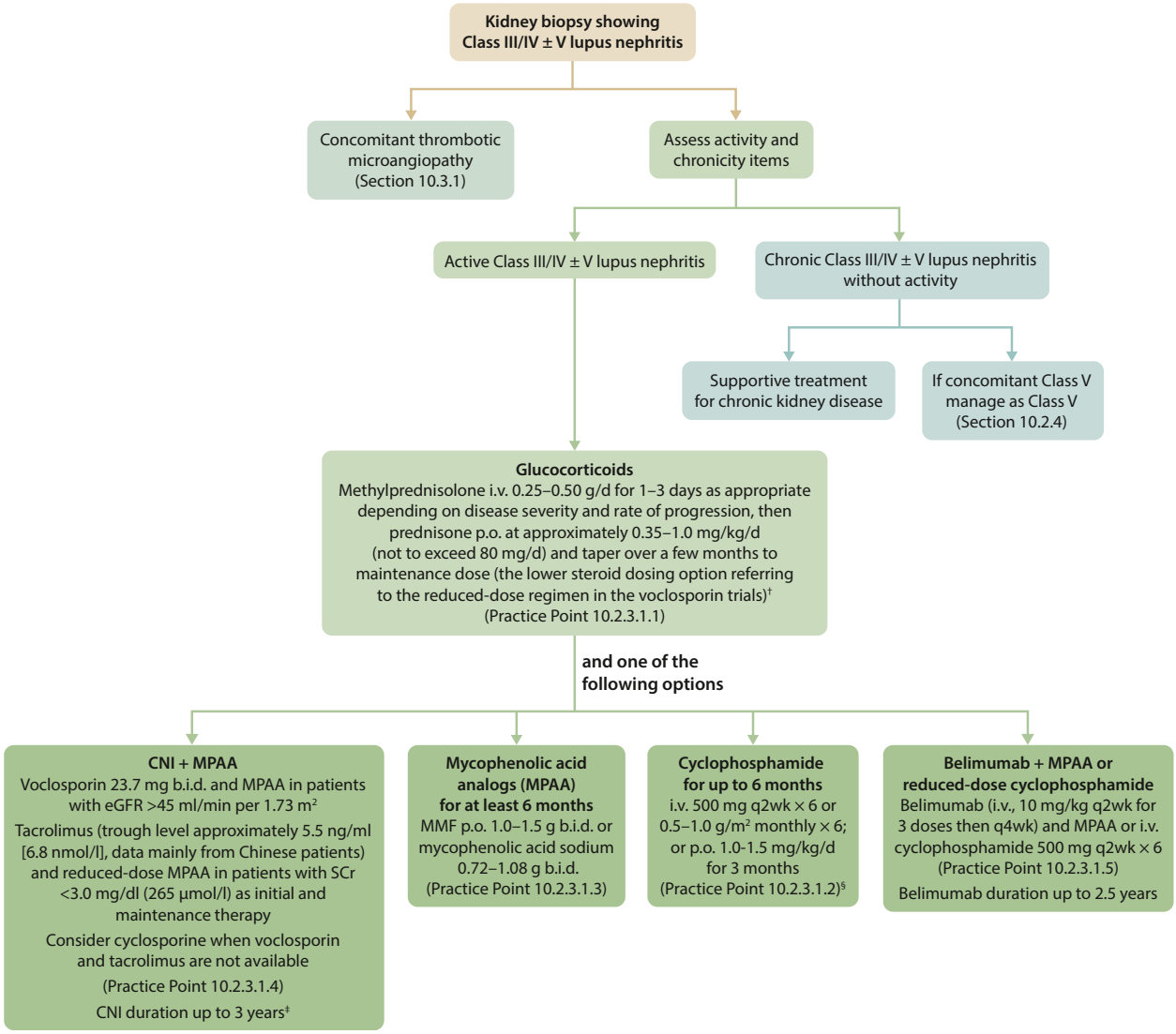


**Figure 6.** Recommended approach for initial therapy of active class III/IV lupus nephritis. Caution is warranted when CNIs are used in patients with significantly impaired kidney function, in view of increased susceptibility for severe consequences due to CNI nephrotoxicity. The estimated glomerular filtration rate and serum creatinine levels stated in the figure were patient selection criteria adopted in the respective clinical trials. †Refer to Figure 4 for examples of glucocorticoid treatment regimens. ‡Refer to Figure 9 in the KDIGO guideline for durations of CNI or belimumab treatment in clinical trials. §Refer to Figure 7 for comments on cyclophosphamide regimens. (Note: Chapter 5 refers to chapter 5 of the KDIGO Guideline on Glomerular Diseases.) Abbreviations: b.i.d., twice daily; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil; MPAA, mycophenolic acid analog; p.o., oral; q2wk, every 2 weeks; q4wk, every 4 weeks; s.c., subcutaneous; SCr, serum creatinine.

prednisone is commonly employed in practice. Additionally, most patients want to avoid high-dose corticosteroids given their side effects; accommodating this preference is a persistent therapeutic challenge for nephrologists. More data on low-dose steroid regimens and their combinations with newer therapeutic options are needed. Because SLE disproportionately affects women of childbearing age, the limited data guiding the management of LN during pregnancy is a critical gap; therapeutic strategies in this setting are often informed primarily by expert opinion. Unfortunately, pregnancy and active breastfeeding are considered exclusion criteria in most LN clinical trials, so uncertainty persists about how best to manage active LN during these periods.

A wide range of factors plays a role in treatment decisions for LN, which should be individualized based on biopsy findings, pertinent biomarkers and laboratory results, and patient characteristics, including extrarenal manifestations of lupus. Notably, biomarkers such as TIMP-1, OPG, CD163, CP, and RBP4 are currently at early stages of evaluation for the early detection of LN.[8] Although the guidelines offer general plans and recommendations, management of LN has moved toward more individualized treatment, especially in centers with dedicated glomerular disease clinics.

| | High-dose intravenous cyclophosphamide (NIH regimen) | Low-dose intravenous cyclophosphamide (Euro-Lupus regimen) | Oral cyclophosphamide |
|---|---|---|---|
| **Cyclophosphamide** | i.v. 0.5–1 g/m$^2$ monthly for 6 months | i.v. 500 mg every 2 weeks for 3 months | p.o. 1.0–1.5 mg/kg/d (max 150 mg/d) for 2–6 months |
| **Comments** | Efficacy data included patients of different races/ethnicities | Efficacy data mainly in Caucasian patients, with some data from patients of African or Caribbean descent, Hispanic descent, Indian patients, and other Asian countries | Efficacy data included patients of different races/ethnicities |

**Figure 7.** Cyclophosphamide dosing regimens, combined with glucocorticoids, in initial treatment for active class III/IV lupus nephritis. Abbreviations: i.v., intravenous; max, maximum; NIH, National Institutes of Health; p.o., oral.

### *10.2.3.2. Maintenance Therapy for Class III and Class IV Lupus Nephritis*

**Recommendation 10.2.3.2.1: We recommend that after completion of initial therapy, patients should be placed on MPAA for maintenance (*1B*).**

Practice Point 10.2.3.2.1: Azathioprine is an alternative to MPAA after completion of initial therapy in patients who do not tolerate MPAA, who do not have access to MPAA, or who are considering pregnancy.

Practice Point 10.2.3.2.2: Glucocorticoids should be tapered to the lowest possible dose during maintenance, except when glucocorticoids are required for extrarenal lupus manifestations; discontinuation of glucocorticoids can be considered after patients have maintained a complete clinical renal response for ≥12 months.

Practice Point 10.2.3.2.3: The dose of mycophenolate mofetil (MMF) in the early maintenance phase is approximately 750–1000 mg twice daily, and for mycophenolic acid (MPA), approximately 540–720 mg twice daily.

Practice Point 10.2.3.2.4: The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should be ≥36 months.

Practice Point 10.2.3.2.5: Patients treated with triple immunosuppressive regimens that include belimumab or a CNI in addition to standard immunosuppressive therapy can continue with a triple immunosuppressive regimen as maintenance therapy (Figure 9 [in the KDIGO guideline]).

Practice Point 10.2.3.2.6: If MPAA and azathioprine cannot be used for maintenance, CNIs or mizoribine or leflunomide can be considered (Figure 9 [in the KDIGO guideline]).

***Commentary.*** Following a short-term immunosuppressive induction therapy, the incidence of relapse of LN can be as high as 60% in patients with severe forms of LN when only corticosteroids are used for maintenance therapy. Therefore, the KDIGO guideline appropriately recommends a maintenance immunosuppression regimen to consolidate and sustain the response in patients with partial and complete remission.

***Clinical Utility.*** The main goal of maintenance immunosuppressive therapy is to prevent relapses without excessive risk of SAEs. We agree with Recommendation 10.2.3.2.1 to use MPAA as the first-choice immunosuppressive maintenance therapy, and Practice Point 10.2.3.2.3 to treat with either MMF between 750 and 1,000 mg twice daily or MPA between 540 and 720 mg twice daily, with the lowest possible dose of corticosteroids. The second-choice agent for maintenance therapy is azathioprine (AZA) between 1 and 2 mg/kg daily. KDIGO recommends MPAA as the first-choice maintenance therapy because MMF compared to AZA was associated with a lower incidence of relapses (13% to 19% vs 23% to 25%)[9,10] and with a lower incidence of SAEs (24% to 25% vs 31% to 33%)[9,10] in randomized controlled trials (RCTs) with long-term follow-up between 3 and 4 years. Fortunately, the cost of MPAA has declined in the United States, making MPAA affordability almost comparable to AZA. KDIGO recommends maintenance therapy with AZA as an alternative to MPAA in patients considering pregnancy or in those with intolerance or lack of access to MPAA.

The alternative maintenance immunosuppressive therapies are CNIs, mizoribine and leflunomide. We recommend a cautious approach to the use of CNIs as long-term maintenance therapy due to the risk of irreversible nephrotoxicity, first described in kidney biopsies of recipients of organ transplants.[11,12] The use of a triple immunosuppressive regimen as maintenance, such as the use of a CNI or belimumab with a MPAA or AZA and corticosteroids, has been reported in post hoc analyses of participants in induction RCTs of triple immunosuppressive regimens for severe LN. These analyses selected participants who did well to continue triple immunosuppressive regimens for an extended follow-up period, but excluded participants who dropped out due to lack of response, treatment intolerance, or onset of SAEs; therefore, these post hoc analyses introduced selection bias that overestimated the benefit and

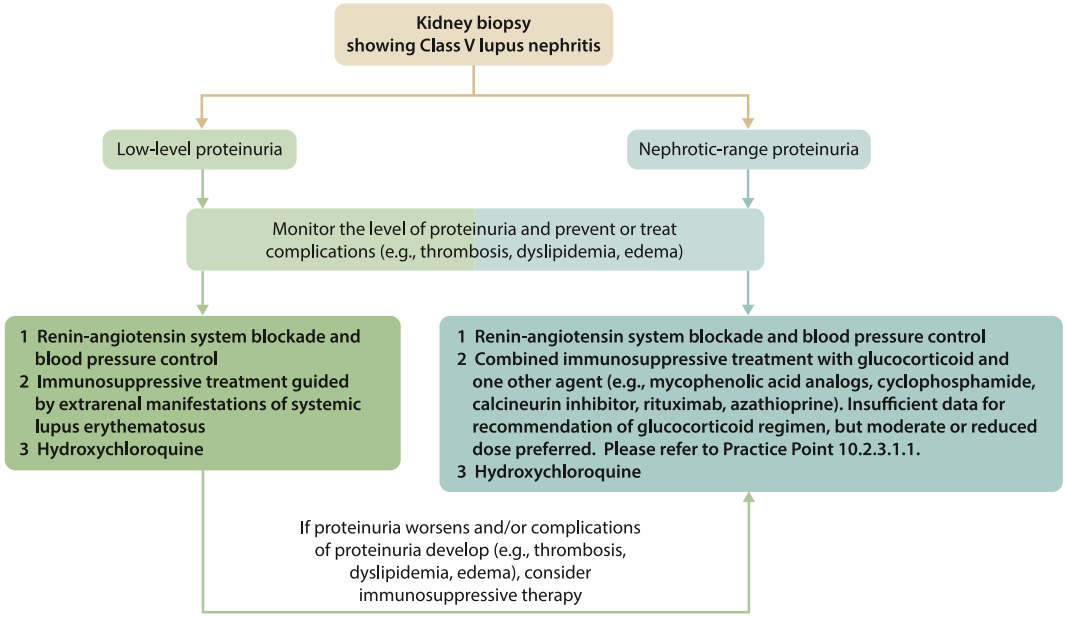


**Figure 8.** Management of patients with pure class V lupus nephritis.

underestimated the risk of triple immunosuppressive regimens used for maintenance therapy. We recommend a cautious approach to the use of a triple immunosuppressive regimen for maintenance therapy due to the risk of over-immunosuppression compared with using a double immunosuppressive maintenance regimen.

The long-term use of cyclophosphamide as maintenance therapy is no longer recommended due to the high risk of SAEs associated with cumulative cyclophosphamide doses. Practice Point 10.2.3.2.2 appropriately recommends the use of the lowest possible dose of corticosteroids during maintenance therapy to also reduce the risk of SAEs associated with the high cumulative dose of corticosteroids.

***Implementation and Challenges.*** There are challenges when recommending the use of immunosuppressive regimens for long-term maintenance therapy, including nonadherence to daily dosing and the increased cost. In patients with LN, nonadherence to immunosuppressive regimens has been reported to be as high as 65% and is associated with a 4.9 higher risk of developing more than one LN relapse. The cost of medications, forgetfulness, and the occurrence of side effects have contributed to nonadherence.[13]

Another challenge is the best timing to discontinue long-term maintenance immunosuppression therapy. A beneficial long-term maintenance immunosuppression therapy must reduce the risk of relapses without increasing the risk of adverse events. In the Win-Lupus RCT, patients with clinically complete or partial remission of severe LN for a sustained time of 24 to 36 months and on stable maintenance immunosuppressive therapy (MMF or AZA) were randomized to either discontinue or continue immunosuppressive therapy. The patients who discontinued maintenance immunosuppressive therapy had a higher incidence of LN relapses (27.3%) compared with the patients who continued immunosuppressive therapy (12.5%), without differences in the incidence of adverse events.[14] Additionally, studies of patients with LN who undergo serial biopsies have demonstrated that despite 36 months of immunosuppression and 12 months of sustained complete clinical LN remission, 28% to 50% of patients still showed histologic activity on kidney biopsies that would increase the risk of relapses if the maintenance immunosuppression were discontinued[15-17]; therefore, we recommend maintenance immunosuppressive therapy with a total duration of at least 36 months, and potentially longer than 36 months in populations with a high risk for poor outcomes, as long as patients remain free of SAEs. We also consider the kidney biopsy to be the best diagnostic test to ascertain histologically sustained remission of LN to determine the best time of discontinuing long-term maintenance immunosuppressive therapy. The kidney biopsy can also help to ascertain whether persistent proteinuria and/or reduced eGFR are due to inactive chronic LN that would not benefit from long-term immunosuppression.

### 10.2.4. Class V Lupus Nephritis

Practice Point 10.2.4.1: A suggested approach to the management of patients with pure Class V LN is described in Figure 8 [Fig 10 in the KDIGO guideline].

***Commentary and Clinical Utility.*** The management of LN class V largely depends on the level of proteinuria. For patients with nephrotic range proteinuria, in addition to the standard care such as renin-angiotensin-aldosterone system inhibition and blood pressure management,

treatment includes combined immunosuppressive therapy using corticosteroids with another immunosuppressive agent. Although consensus is lacking on the optimal steroid dose in this setting, moderate to low doses are generally preferred. For patients with subnephrotic range proteinuria, the decision to initiate immunosuppressive therapy would be guided by the presence and severity of extrarenal manifestations (Fig 8 [Fig 10 in the KDIGO guideline]).

## 10.2.5. Response and Relapse Considerations

### 10.2.5.1. Assessing Treatment Response in LN

Practice Point 10.2.5.1.1: Definitions of response to therapy in LN used in clinical trials are provided in Figure 9 [Fig 11 in the KDIGO guideline].

### 10.2.5.2. Management of Unsatisfactory Response to Treatment

Practice Point 10.2.5.2.1: An algorithmic approach to patients whose response to therapy is deemed unsatisfactory is provided in Figure 10 [Fig 12 in the KDIGO guideline].

### 10.2.5.3. Treatment of LN Relapse

Practice Point 10.2.5.3.1: After a complete or partial remission has been achieved, LN relapse should be treated with the same initial therapy used to achieve the original response, or an alternative recommended therapy.

***Commentary and Clinical Utility.*** Figure 9 (Fig 11 in the KDIGO guideline) summarizes the definitions of treatment response in LN. At one end of the spectrum is a *complete response* characterized by a reduction in proteinuria to below 0.5 g/g and stabilization of kidney function within ±10% to 15% of baseline, typically achieved within 6 to 12 months of therapy initiation. However, the KDIGO guideline notes that complete response may take longer than 12 months in some patients. This is important because more time is usually allowed to achieve complete remission so long as the patient's laboratory and clinical results are both moving toward the treatment goals. The other extreme is *no kidney response*, defined as the failure to achieve either a partial or complete renal response within 6 to 12 months of starting treatment.

For patients who demonstrate an unsatisfactory response to therapy, the KDIGO guideline recommends a stepwise approach as shown in Figure 10 (Fig 12 in the KDIGO guideline). The first step is to confirm if the patient is medication adherent; if so, the next consideration is whether target plasma drug levels have been achieved. When the drug levels are appropriate yet the response remains suboptimal, a repeat kidney biopsy may be useful. This helps determine whether persistent proteinuria is driven by chronic damage or by another underlying process, such as thrombotic microangiopathy. If active disease is confirmed, switching to an alternative immunosuppressive agent should be considered. Additional options include the use of rituximab or participation in clinical trials exploring novel therapeutic strategies such as chimeric antigen receptor (CAR) T-cell studies.[18,19]

Clinical trials focused on CAR-T gained significant momentum following the 2022 landmark compassionate-use

| Criteria | Definition |
|---|---|
| **Complete response*** | • Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection<br>• Stabilization or improvement in kidney function (±10%–15% of baseline)<br>• Within 6–12 mo of starting therapy, but could take more than 12 mo |
| **Primary efficacy renal response** | • PCR ≤0.7 g/g (70 mg/mmol)<br>• eGFR that was no worse than 20% below the pre-flare value or ≥60 ml/min per 1.73 $m^2$<br>• No use of rescue therapy for treatment failure |
| **Partial response** | • Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection<br>• Stabilization or improvement in kidney function (±10%–15% of baseline)<br>• Within 6–12 mo of starting therapy |
| **No kidney response** | • Failure to achieve a partial or complete response within 6–12 mo of starting therapy |

**Figure 9.** Definitions of response commonly used in clinical trials of lupus nephritis. *For children < 18 years old, complete response is defined as proteinuria < 0.5 g/1.73 $m^2$ per day or <300 mg/$m^2$ per day based on a 24-hour urine specimen. Abbreviations: eGFR, estimated glomerular filtration rate; PCR, protein-creatinine ratio.

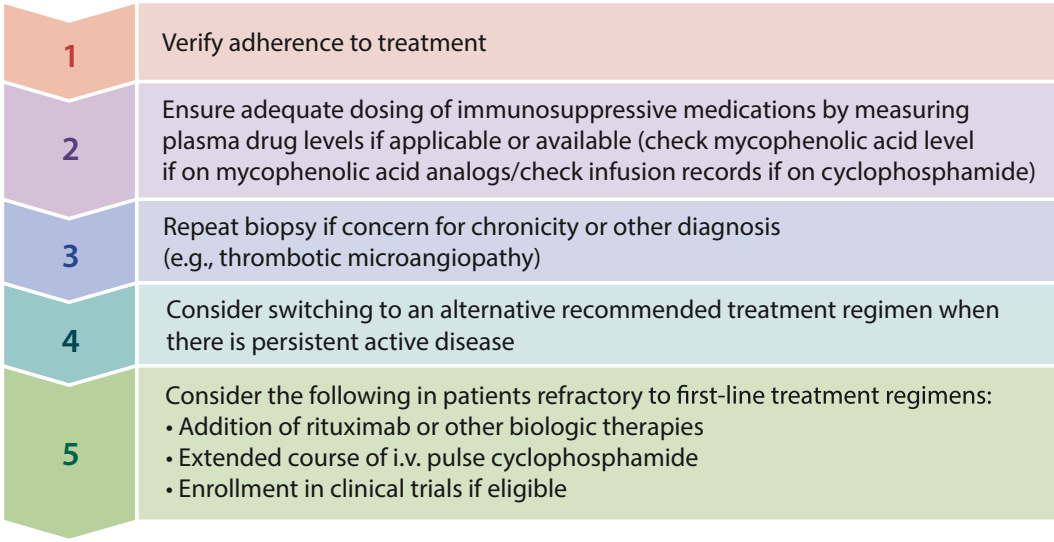


**Figure 10.** Management of patients who show unsatisfactory response to initial therapy for active lupus nephritis. Abbreviations: i.v., intravenous.

report of 5 patients with refractory SLE who were treated with CD19-targeted CAR T cells (anti-CD19 CAR-T).[19] All 5 patients achieved drug-free remission, with sustained B-cell aplasia and no recurrence of disease activity over the follow-up period; this study served as a proof of concept of a potential treatment option in refractory cases. Currently, in the United States the majority of CAR T-cell trials targeting autoimmune diseases are in early phase development, predominantly phase 1 or phase 1/2 designs focusing on dose escalation, safety profiling, and preliminary efficacy signals.[20] Hence, at the time of writing no CAR-T-cell therapy has received FDA approval for SLE or LN, and CAR-T continues to be available only through clinical trials to a highly selective group of patients. Navigating safety, high cost, and lack of long term follow up data on the CAR-T studies remains a challenge and needs further data.

## 10.3. Special Situations

### 10.3.1. Lupus Nephritis and Thrombotic Microangiopathy

Practice Point 10.3.1.1: Patients with LN and thrombotic microangiopathy (TMA) should be managed according to the underlying etiology of TMA, as shown in Figure 11 [Fig 13 in the KDIGO guideline].[21]

#### *Commentary and Clinical Utility*

In patients with suspected thrombotic microangiopathy in addition to LN, the KDIGO guideline recommends assessing ADAMTS13 activity and testing antibodies to ADAMTS13 and phospholipids, as well as calculating the PLASMIC score. The PLASMIC score incorporates platelet count, evidence of hemolysis, presence of active cancer, history of transplantation, mean corpuscular volume (MCV), international normalized ratio (INR), and serum creatinine level. A low score (≤4) suggests that alternative diagnoses are more likely.[22]

The KDOQI work group agrees with the KDIGO guideline authors that when the clinical suspicion is high—reflected by a high PLASMIC score (≥5)—plasma exchange and glucocorticoid therapy should be initiated promptly while waiting for the results. In practice, access to specialized assays may be limited, and the results can be delayed; however, this should not postpone appropriate treatment when the likelihood of thrombotic microangiopathy is significant. The treatment approach based on ADAMTS13 results is summarized in Figure 11 (Fig 13 in the KDIGO guideline).

### 10.3.2. Pregnancy in Patients With Lupus Nephritis

Practice Point 10.3.2.1: Patients with active LN should be counseled to avoid pregnancy while the disease is active or when treatment with potentially teratogenic drugs is ongoing, and for ≥6 months after LN becomes inactive.

Practice Point 10.3.2.2: To reduce the risk of pregnancy complications, hydroxychloroquine should be continued during pregnancy, and low-dose aspirin should be started before 16 weeks of gestation.

Practice Point 10.3.2.3: Glucocorticoids, hydroxychloroquine, azathioprine, tacrolimus, and cyclosporine are considered safe immunosuppressive treatments during pregnancy.

#### *Commentary and Clinical Utility*

We agree with the recommendation regarding pregnancy planning once LN has been inactive for at least 6 months. Pregnancies in patients with a history of LN should ideally

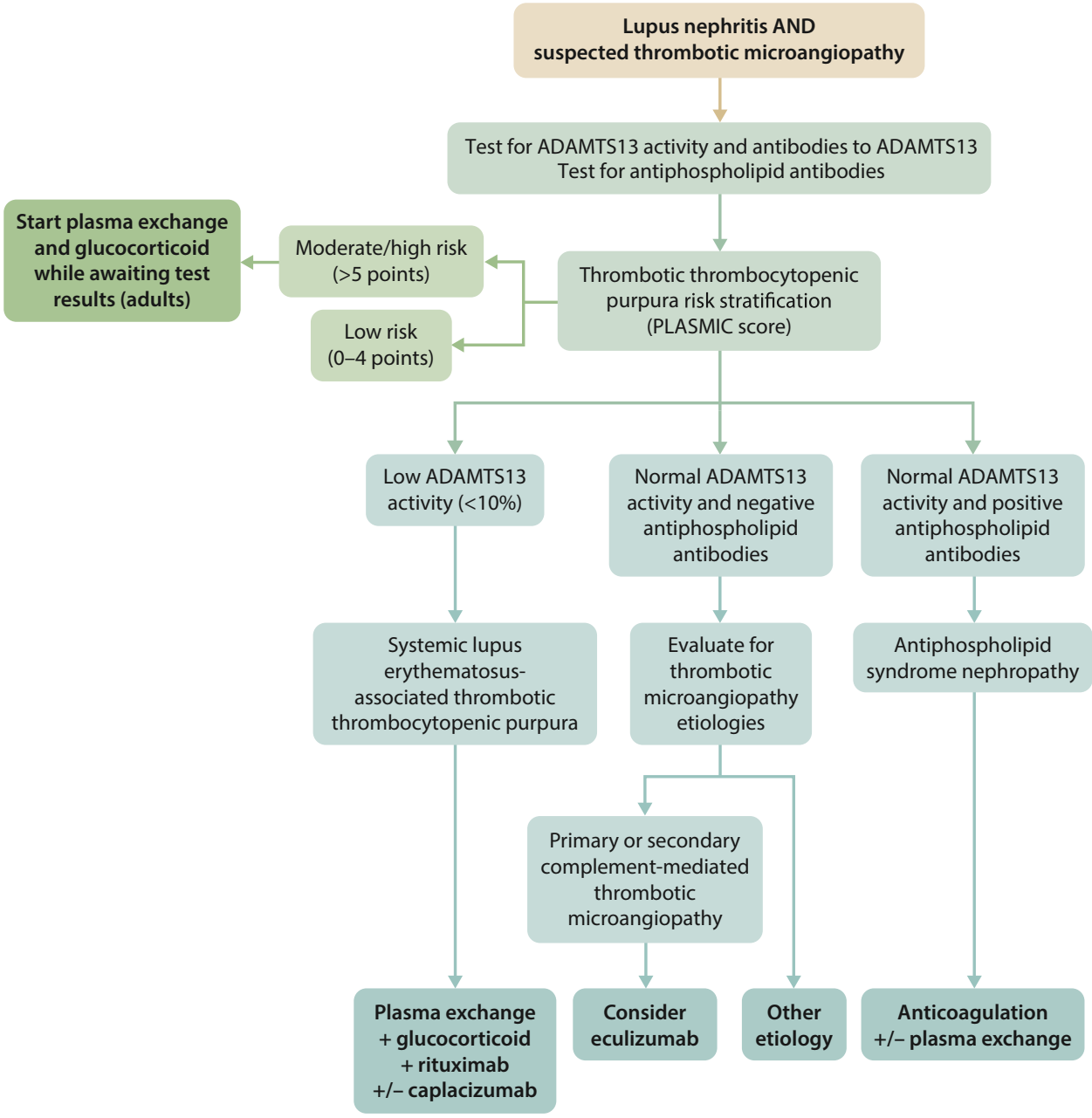


**Figure 11.** Management of patients with lupus nephritis and thrombotic microangiopathy (TMA). Based on information in Bendapudi et al.[21] Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PLASMIC, platelet count, combined hemolysis variable, absence of active cancer, absence of stem-cell or solid-organ transplant, mean corpuscular volume (MCV), international normalized ratio (INR), creatinine.

be managed by a multidisciplinary team that includes nephrologists, rheumatologists, obstetricians, and maternal-fetal medicine to optimize outcomes. Hydroxychloroquine is recommended to be continued during pregnancy to decrease the risk of flares, and this approach has also been endorsed in the European Alliance of Associations for Rheumatology (EULAR) guidelines. We agree that glucocorticoids, azathioprine, cyclosporine, and tacrolimus (with close monitoring of therapeutic levels) are safe to treat active disease during pregnancy.

### 10.3.3. Treatment of Lupus Nephritis in Children

Practice Point 10.3.3.1: Treat pediatric patients with LN using immunosuppression regimens similar to those used in adults, but consider issues relevant to this population,

such as dose adjustment, growth, fertility, and psychosocial factors, when devising the therapy plan.

### Commentary

We agree with Practice Point 10.3.3.1 that, for patients transitioning to adult nephrology care, a close collaboration between pediatric and adult nephrologists is recommended.

## 10.3.4. Management of Lupus Patients With Kidney Failure

Practice Point 10.3.4.1: Patients with LN who develop kidney failure may be treated with hemodialysis, peritoneal dialysis, or kidney transplantation; and kidney transplantation is preferred to long-term dialysis.

### Commentary

Major advances in early diagnosis, classification, and immunosuppressive therapies for patients with LN have resulted in a significant improvement in patient survival; however, approximately 10% of patients with LN still develop ESKD. When patients with LN approach ESKD, patients and providers must choose among the available KRT options. Many more patients with LN and ESKD receive dialysis compared with a kidney transplant as their KRT.[23] Preemptive kidney transplantation (PKT) is the preferred treatment for patients with LN approaching the need for KRT, based on recent studies reporting good outcomes[24,25]; however, in the United States fewer than 5% of LN patients with ESKD receive PKT. In a recent study, we reported that the PKT trend has increased minimally in patients with LN from 3.02% in 1985 to only 4.65% in 2019, despite kidney allograft failure (KAF) and mortality risks being similarly low and comparable with those of young recipients of PKT due to other causes of ESKD.[25] Patients with LN who receive a kidney transplant early after initiating dialysis also have significantly lower risk of KAF and mortality compared to those remaining on dialysis.[26]

### Clinical Utility

We agree with Practice Point 10.3.4.1 recommending kidney transplantation as the preferred KRT option as early as possible for patients with ESKD due to lupus.[25-27] In terms of outcomes by initial dialysis modality for patients with LN and ESKD, a large observational study reported similar 3-year survival rates and mortality due to cardiovascular or infectious complications in those receiving peritoneal dialysis and those receiving hemodialysis.[28] However, given the risk of recurrent vascular access thrombosis, we recommend peritoneal dialysis as the preferred modality in patients who are prone to thrombosis.

### Implementation and Challenges

In LN patients with ESKD, achieving higher rates of PKT and early kidney transplantation after starting KRT with dialysis is hindered by frequently delaying kidney transplantation until lupus activity is clinically quiescent and maintenance immunosuppression is minimal or discontinued. It is very likely that in patients with LN and ESKD who have major extrarenal organ activity, delaying kidney transplantation lowers the risk of KAF, mortality, and recurrent LN. By contrast, delaying kidney transplantation in lupus patients with mild to moderate extrarenal clinical and/or immunological activity (low complement component levels or high anti-dsDNA level) can only decrease the trend of PKT and early kidney transplantation after starting with dialysis. Recent studies reported that persistent mild to moderate extrarenal clinical and/or immunological lupus activity at the time of kidney transplantation is not associated with high risk of poor outcomes.[29,30] In the United States, another challenge to implementing higher rates of kidney transplantation is the lack of insurance coverage for many patients with LN and ESKD. The availability of insurance, particularly private insurance, increases the likelihood of kidney transplantation in the United States.[25]

## Conclusion

The management of LN is rapidly evolving. Combination therapy is the cornerstone of LN treatment and avoiding high-dose steroids, when possible, is considered essential. Current research is evaluating a range of biomarkers to address the unmet need to track disease activity, inform management, and limit repeat biopsies. Addressing barriers to treatment adherence is crucial and has been recommended as the first step when approaching patients with an unsatisfactory response to therapy. Future clinical trials should prioritize patient-reported outcomes and incorporate comprehensive assessments of medication tolerability because combination therapy can be challenging to tolerate and affect quality of life.

For all patients with SLE and LN, particularly women of childbearing age, a shared decision-making model is essential to develop practical, evidence-based treatment strategies. Furthermore, the management of LN during pregnancy warrants more clinical research and possibly clinical trials to improve management while limiting treatment side effects. The recent FDA approval of obinutuzumab provides another therapeutic option for people with LN. Although emerging CAR T-cell therapies offer promising results, additional data are required to define their long-term efficacy and safety.

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## References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 clinical practice guideline for the management of lupus nephritis. *Kidney Int*. 2024;105(1)(suppl):S1-S69. doi:10.1016/j.kint.2023.09.002
2. Heidenreich U, Mayer G, Herold M, Klotz W, Stempfl Al-Jazrawi K, Lhotta K. Sensitivity and specificity of autoantibody tests in the differential diagnosis of lupus nephritis. *Lupus*. 2009;18(14):1276-1280. doi:10.1177/0961203309345753
3. Sammaritano LR, Askanase A, Bermas BL, et al. 2024 American College of Rheumatology (ACR) guideline for the screening, treatment, and management of lupus nephritis. *Arthritis Rheumatol*. 2025;77(9):1115-1135. doi:10.1002/art.43212
4. Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. *Ann Intern Med*. 2015;162(1):18-26. doi:10.7326/m14-1030
5. 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;397(10289):2070-2080. doi:10.1016/s0140-6736(21)00578-x
6. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med*. 2020;383(12):1117-1128. doi:10.1056/NEJMoa2001180
7. Furie RA, Rovin BH, Garg JP, et al. Efficacy and safety of obinutuzumab in active lupus nephritis. *N Engl J Med*. 2025;392(15):1471-1483. doi:10.1056/NEJMoa2410965
8. Vodehnal S, Mohan C. Urinary biomarkers for active lupus nephritis that have survived independent validation across cohorts. *Kidney Int*. 2024;106(6):1135-1145. doi:10.1016/j.kint.2024.09.007
9. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med*. 2011;365(20):1886-1895. doi:10.1056/NEJMoa1014460
10. Houssiau FA, D'Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis*. 2010;69(12):2083-2089. doi:10.1136/ard.2010.131995
11. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. *N Engl J Med*. 2003;349(24):2326-2333. doi:10.1056/NEJMoa020009
12. Myers BD, Ross J, Newton L, Luetscher J, Perlroth M. Cyclosporine-associated chronic nephropathy. *N Engl J Med*. 1984;311(11):699-705. doi:10.1056/nejm198409133111103
13. Ali AY, Abdelaziz TS, Behiry ME. The prevalence and causes of non-adherence to immunosuppressive medications in patients with lupus nephritis flares. *Curr Rheumatol Rev*. 2020;16(3):245-248. doi:10.2174/1573397115666190626111847
14. Jourde-Chiche N, Costedoat-Chalumeau N, Baumstarck K, et al. Weaning of maintenance immunosuppressive therapy in lupus nephritis (WIN-Lupus): results of a multicentre randomised controlled trial. *Ann Rheum Dis*. 2022;81(10):1420-1427. doi:10.1136/annrheumdis-2022-222435
15. Alvarado AS, Malvar A, Lococo B, et al. The value of repeat kidney biopsy in quiescent Argentinian lupus nephritis patients. *Lupus*. 2014;23(8):840-847. doi:10.1177/0961203313518625
16. 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(4):788-794. doi:10.1016/j.kint.2018.05.021
17. Malvar A, Alberton V, Lococo B, et al. Kidney biopsy-based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis. *Kidney Int*. 2020;97(1):156-162. doi:10.1016/j.kint.2019.07.018
18. Krickau T, Naumann-Bartsch N, Aigner M, et al. CAR T-cell therapy rescues adolescent with rapidly progressive lupus nephritis from haemodialysis. *Lancet*. 2024;403(10437):1627-1630. doi:10.1016/S0140-6736(24)00424-0
19. Mackensen A, Müller F, Mougiakakos D, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat Med*. 2022;28(10):2124-2132. doi:10.1038/s41591-022-02017-5
20. Matarneh A, Matarneh B, Salameh O, Akkari A, Ghahramani N, Trivedi N. Chimeric antigen receptor T cell therapy in systemic lupus erythematosus: mechanisms, clinical advances, and future directions a comprehensive review. *Clin Rev Allergy Immunol*. 2025;68(1):103. doi:10.1007/s12016-025-09114-6
21. Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol*. 2017;4(4):e157-e164. doi:10.1016/s2352-3026(17)30026-1
22. Upadhyay VA, Geisler BP, Sun L, et al. Utilizing a PLASMIC score-based approach in the management of suspected immune thrombotic thrombocytopenic purpura: a cost minimization analysis within the Harvard TMA Research Collaborative. *Br J Haematol*. 2019;186(3):490-498. doi:10.1111/bjh.15932
23. Costenbader KH, Desai A, Alarcón GS, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease

due to lupus nephritis in the US from 1995 to 2006. *Arthritis Rheum*. 2011;63(6):1681-1688. doi:10.1002/art.30293
24. Naveed A, Nilubol C, Melancon JK, Girlanda R, Johnson L, Javaid B. Preemptive kidney transplantation in systemic lupus erythematosus. *Transplant Proc*. 2011;43(10):3713-3714. doi:10.1016/j.transproceed.2011.08.092
25. Contreras G, Pagan J, Elfassy T, et al. Trends of preemptive kidney transplantation in lupus compared to other primary diseases leading to end stage kidney disease in the United States of America. *Lupus*. 2025;34(8):775-786. doi:10.1177/09612033251344189
26. Jorge A, Wallace ZS, Lu N, Zhang Y, Choi HK. Renal transplantation and survival among patients with lupus nephritis: a cohort study. *Ann Intern Med*. 2019;170(4):240-247. doi:10.7326/m18-1570
27. Plantinga LC, Patzer RE, Drenkard C, et al. Association of time to kidney transplantation with graft failure among U.S. patients with end-stage renal disease due to lupus nephritis. *Arthritis Care Res (Hoboken)*. 2015;67(4):571-581. doi:10.1002/acr.22482
28. Contreras G, Pagan J, Chokshi R, et al. Comparison of mortality of ESRD patients with lupus by initial dialysis modality. *Clin J Am Soc Nephrol*. 2014;9(11):1949-1956. doi:10.2215/cjn.02500314
29. Chung MC, Yu TM, Shu KH, et al. Influence of pre-transplantation dialysis time and lupus activity on outcome of kidney transplantation in systemic lupus erythematosus. *Transplant Proc*. 2014;46(2):336-338. doi:10.1016/j.transproceed.2013.11.085
30. Yap KS, Urowitz MB, Mahood Q, et al. The utility of lupus serology in predicting outcomes of renal transplantation in lupus patients: systematic literature review and analysis of the Toronto lupus cohort. *Semin Arthritis Rheum*. 2017;46(6):791-797. doi:10.1016/j.semarthrit.2016.09.008