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cyclophosphamide versus induction: prednisone

cyclophosphamide versus induction: prednisone

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REFERENCE KEYS

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as Level 1 or Level 2, and the quality of the supporting evidence is shown as A, B, C, or D.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Implications</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Clinicians</td>
</tr>
<tr>
<td></td>
<td>Most people in your situation would want the recommended course of action, and only a small proportion would not.</td>
<td>Most patients should receive the recommended course of action.</td>
</tr>
<tr>
<td>Level 1</td>
<td>“We recommend”</td>
<td>The recommendation can be evaluated as a candidate for developing a policy or a performance measure.</td>
</tr>
<tr>
<td></td>
<td>The majority of people in your situation would want the recommended course of action, but many would not.</td>
<td>Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.</td>
</tr>
<tr>
<td>Level 2</td>
<td>“We suggest”</td>
<td>The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Quality of evidence</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effect is close to the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>The estimate of the effect is very uncertain, and often it will be far from the true effect.</td>
</tr>
</tbody>
</table>
CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA.

<table>
<thead>
<tr>
<th>Persistent albuminuria categories</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description and range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal to mildly increased</td>
<td>&lt; 30 mg/g</td>
<td>30–300 mg/g</td>
<td>&gt; 300 mg/g</td>
</tr>
<tr>
<td>Moderately increased</td>
<td>&lt; 3 mg/mmol</td>
<td>3–30 mg/mmol</td>
<td>&gt; 30 mg/mmol</td>
</tr>
</tbody>
</table>

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Green, low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

GFR, glomerular filtration rate
## Conversion Factors of Conventional Units to SI Units

<table>
<thead>
<tr>
<th>Conventional unit</th>
<th>Conversion factor</th>
<th>SI Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin g/dl</td>
<td>10</td>
<td>g/l</td>
</tr>
<tr>
<td>Creatinine mg/dl</td>
<td>88.4</td>
<td>µmol/l</td>
</tr>
<tr>
<td>Creatinine clearance ml/min</td>
<td>0.01667</td>
<td>ml/s</td>
</tr>
<tr>
<td>Cyclosporine ng/ml</td>
<td>0.832</td>
<td>--</td>
</tr>
<tr>
<td>PCR  mg/g</td>
<td>0.113</td>
<td>mg/mmol</td>
</tr>
</tbody>
</table>

Note: Conventional unit x conversion factor = SI unit

## Albuminuria Categories in CKD

<table>
<thead>
<tr>
<th>Category</th>
<th>AER (mg/24 hours)</th>
<th>ACR (approximate equivalent) (mg/mmol)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt;30</td>
<td>&lt;3</td>
<td>&lt;30</td>
</tr>
<tr>
<td>A2</td>
<td>30-300</td>
<td>3-30</td>
<td>30-300</td>
</tr>
<tr>
<td>A3</td>
<td>&gt;300</td>
<td>&gt;30</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

*Relative to young adult level

ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease
ABBREVIATIONS AND ACRONYMS

aPLA  antiphospholipid antibodies
APS  antiphospholipid syndrome
CFH  Complement Factor H
CFHR  Complement Factor H–related
CI  confidence interval
CKD  chronic kidney disease
CNI  calcineurin inhibitor
CV  cardiovascular
dsDNA  double-stranded DNA
eGFR  estimated glomerular filtration rate
FDA  Food and Drug Administration
FSGS  focal segmental glomerulosclerosis
G6PD  glucose-6-phosphate dehydrogenase
GN  glomerulonephritis
HBV  hepatitis B virus
HCV  hepatitis C virus
HIV  human immunodeficiency virus
HR  hazard ratio
i.v.  intravenous
KDIGO  Kidney Disease: Improving Global Outcomes
LN  lupus nephritis
MCD  minimal change disease
MPA  mycophenolic acid
MPAA  mycophenolic acid analogs
MMF  mycophenolate mofetil
NIH  National Institutes of Health, USA
OR  odds ratio
PCR  protein–creatinine ratio
PERR  Primary Efficacy Renal Response
p.o.  oral
RAS(i)  renin–angiotensin system (inhibitor)
RCT  randomized controlled trial
s.c.  subcutaneous
SCr  serum creatinine
SLE  systemic lupus erythematosus
TGA  Therapeutics Goods Administration
TMA  thrombotic microangiopathy
TMP-SMX  trimethoprim/sulfamethoxazole
U.S.  United States
NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in July 2022. It is designed to assist decision-making. It is not intended to define a standard of care, and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members’ Disclosure section and is kept on file at KDIGO.

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The Kidney Disease: Improving Global Outcomes (KDIGO) 2023 Clinical Practice Guideline for Lupus Nephritis represents a focused update of Chapter 10: Lupus nephritis from the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. The aim is to assist clinicians caring for individuals with lupus nephritis. The update takes into consideration evidence from randomized controlled trials published since February 2022. As in 2021, the chapter follows the same template providing guidance related to diagnosis, treatment, and special situations. Based on the evidence, this update is mostly related to the guidance related to treatment of lupus nephritis.

Development of this guideline update followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the quality of the evidence and the strength of recommendations followed the “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) approach. Limitations of the evidence are discussed and areas of future research are also presented.

**Keywords:** evidence-based; glomerular diseases; glomerulonephritis; guideline; KDIGO; lupus nephritis; nephrotic syndrome; systematic review
SUMMARY OF RECOMMENDATION STATEMENTS
AND PRACTICE POINTS

CHAPTER 10. LUPUS NEPHRITIS

10.1 Diagnosis

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

![Flowchart of kidney involvement diagnosis](image)

Figure 1 | Diagnosis of kidney involvement in systemic lupus erythematosus. anti-dsDNA, anti-double-stranded deoxyribonucleic acid; eGFR, estimated glomerular filtration rate.
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 3.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Risk attenuation</th>
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</thead>
<tbody>
<tr>
<td>Cardiovascular risk</td>
<td>• Lifestyle modifications – smoking cessation, body weight optimization, exercise</td>
</tr>
<tr>
<td></td>
<td>• Dyslipidemia management</td>
</tr>
<tr>
<td></td>
<td>• Low-dose aspirin during pregnancy</td>
</tr>
<tr>
<td>Proteinuria (Chapter 1)</td>
<td>• Avoidance of high-sodium diet</td>
</tr>
<tr>
<td></td>
<td>• Blood pressure control</td>
</tr>
<tr>
<td></td>
<td>• RAS blockade</td>
</tr>
<tr>
<td>Infection risk</td>
<td>• Assess medical history of herpes zoster and tuberculosis</td>
</tr>
<tr>
<td></td>
<td>• Screening for HBV, HCV, HIV, and HBV vaccination</td>
</tr>
<tr>
<td></td>
<td>• <em>Pneumocystis jirovecii</em> prophylaxis (issue of potential adverse drug reaction</td>
</tr>
<tr>
<td></td>
<td>discussed below)</td>
</tr>
<tr>
<td></td>
<td>• Influenza and pneumococcal vaccination</td>
</tr>
<tr>
<td></td>
<td>• Individualized consideration for recombinant zoster vaccine</td>
</tr>
<tr>
<td></td>
<td>• Individualized consideration for other infectious organisms as dictated by</td>
</tr>
<tr>
<td></td>
<td>public health concerns at the time of treatment</td>
</tr>
<tr>
<td>Bone injury</td>
<td>• Bone mineral density and fracture risk assessment</td>
</tr>
<tr>
<td></td>
<td>• Calcium and vitamin D supplementation</td>
</tr>
<tr>
<td></td>
<td>• Bisphosphonates when appropriate</td>
</tr>
<tr>
<td>Ultraviolet light</td>
<td>• Broad-spectrum sunscreen</td>
</tr>
<tr>
<td>exposure</td>
<td>• Limit ultraviolet light exposure</td>
</tr>
<tr>
<td>Premature ovarian failure</td>
<td>• Gonadotropin-releasing hormone agonists (i.e. leuprolide)</td>
</tr>
<tr>
<td></td>
<td>• Sperm/oocyte cryopreservation</td>
</tr>
<tr>
<td>Unplanned pregnancy</td>
<td>• Individual evaluation and counselling for contraception type</td>
</tr>
<tr>
<td></td>
<td>(preference, thrombosis risk, age)</td>
</tr>
<tr>
<td>Cancer</td>
<td>• Evaluate individual risk factors for malignancies</td>
</tr>
<tr>
<td></td>
<td>• Age-specific malignancy screening</td>
</tr>
<tr>
<td></td>
<td>• Limit lifetime cyclophosphamide exposure to &lt;36 g</td>
</tr>
</tbody>
</table>

*Figure 3 | Measures to minimize the risk of complications related to lupus nephritis or its treatment. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RAS, renin–angiotensin system.*
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 4)

Figure 4 | Immunosuppressive treatment for patients with Class I or Class II lupus nephritis.

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 either one of the following:

i. mycophenolic acid analogues (MPAA) (IX); or

ii. low-dose intravenous cyclophosphamide (IX); or

iii. belimumab and either MPAA or low-dose intravenous cyclophosphamide (X); or

iv. MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (for example estimated glomerular filtration rate [eGFR] ≤45 ml/min per 1.73 m²) (IX).

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 6).
Practice Point 10.2.3.1.2: Intravenous cyclophosphamide should 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, 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 considered in patients with repeated renal flares or at high-risk for progression to kidney failure.

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.
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 mycophelolic 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 triple immunosuppressive regimen as maintenance therapy (Figure 9).

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).
### Table: Maintenance immunosuppressive regimens in patients with lupus nephritis

<table>
<thead>
<tr>
<th>Maintenance immunosuppressive regimens</th>
<th>Low-dose glucocorticoids AND</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mycophenolic acid analogs</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td>Belimumab and mycophenolic acid analogs or azathioprine</td>
</tr>
<tr>
<td></td>
<td>CNI and mycophenolic acid analogs</td>
</tr>
<tr>
<td></td>
<td>CNI (such as voclosporin, tacrolimus or cyclosporine)</td>
</tr>
<tr>
<td></td>
<td>Mizoribine</td>
</tr>
<tr>
<td>Comments</td>
<td>Preferred treatment based on high-certainty evidence; lower flare rate than azathioprine maintenance</td>
</tr>
<tr>
<td></td>
<td>Low medication cost; safe in pregnancy</td>
</tr>
<tr>
<td></td>
<td>Efficacy and safety of belimumab demonstrated in BLISS-LN (104-wk) and open-label extension trials (28-wk) [Practice Point 10.2.3.2.5]</td>
</tr>
<tr>
<td></td>
<td>Efficacy and safety of voclosporin demonstrated in AURORA 1 (52-wk) and AURORA 2 continuation trials (2-yr); efficacy and safety of tacrolimus demonstrated in ‘Multitarget Therapy’ trial in Chinese patients in which tacrolimus and reduced-dose MPAA were given for 24 months [Practice Point 10.2.3.2.5]</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus and cyclosporine safe in pregnancy; insufficient pregnancy data on voclosporin</td>
</tr>
<tr>
<td></td>
<td>Experience mostly in Japanese patients</td>
</tr>
</tbody>
</table>

**Figure 9 | Maintenance immunosuppressive regimens in patients with lupus nephritis.**

AURORA, Aurinia Renal Response in Active Lupus with Voclosporin; AZA, azathioprine; BLISS-LN, Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis; CNI, calcineurin inhibitor; LN, lupus nephritis; MPAA, mycophenolate acid analogs.

### 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 10.

**Figure 10 | Management of patients with pure Class V lupus nephritis.**
10.2.4.1 Assessing treatment response in LN

Practice Point 10.2.4.1.1: Definitions of response to therapy in LN are provided in Figure 11.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Complete response*  | • Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection  
                      • Stabilization or improvement in kidney function (±10%–15% of baseline)  
                      • Within 6–12 mo of starting therapy, but could take more than 12 mo |
| 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  
                      • Stabilization or improvement in kidney function (±10%–15% of baseline)  
                      • 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 11 | Commonly used definitions of response to therapy in lupus nephritis. *For children <18 years old, complete response is defined as proteinuria <0.5 g/1.73 m²/d or <300 mg/m²/d based on a 24-h urine specimen. PCR, protein–creatinine ratio.

10.2.4.2 Management of unsatisfactory response to treatment

Practice Point 10.2.4.2.1: An algorithmic approach to patients whose response to therapy is deemed unsatisfactory is provided in Figure 12.

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Verify adherence to treatment</td>
</tr>
<tr>
<td>2</td>
<td>Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check-infusion records if on cyclophosphamide)</td>
</tr>
<tr>
<td>3</td>
<td>Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)</td>
</tr>
<tr>
<td>4</td>
<td>Consider switching to an alternative first-line regimen when there is persistent disease activity</td>
</tr>
</tbody>
</table>
| 5      | Consider the following in patients refractory to first-line treatment regimens:  
                      • Addition of rituximab or other biologic therapies  
                      • Extended course of i.v. pulse cyclophosphamide  
                      • Enrollment in clinical trials if eligible |

Figure 12 | Management of patients who show unsatisfactory response to initial therapy for active lupus nephritis. i.v., intravenous.

10.2.4.3 Treatment of LN relapse

Practice Point 10.2.4.3.1: 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 first-line therapy.
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 131.

Figure 13 | Management of patients with lupus nephritis and thrombotic microangiopathy

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: Only glucocorticoids, hydroxychloroquine, azathioprine, tacrolimus, and cyclosporin are considered safe immunosuppressive treatments 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.

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.
CHAPTER 10. LUPUS NEPHRITIS

Among patients with systemic lupus erythematosus (SLE), the reported lifetime incidence of lupus nephritis (LN) is 20%–60%, depending on the demographics of the population studied. Kidney involvement in SLE has been associated with higher mortality, especially for patients progressing to kidney failure. The ultimate goal of treating LN is to preserve kidney function and reduce the morbidity and mortality associated with chronic kidney disease (CKD) and kidney failure, while minimizing medication-associated toxicities.

This chapter makes management recommendations for adults who have SLE with kidney involvement. The focus is on immune complex–mediated glomerulonephritis (GN) in the setting of SLE, commonly referred to as LN, but other types of kidney injury in patients with SLE are also discussed. Information for pediatric populations is limited, but an approach to the management of children with LN is outlined in Practice Point 10.3.3.

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. anti-double-stranded deoxyribonucleic acid; eGFR, estimated glomerular filtration rate.

Patients with SLE should be actively and regularly monitored, as the clinical presentation of kidney involvement can remain silent or asymptomatic for a significant period of time. As the incidence of LN varies by race/ethnicity and age, a high index of suspicion should be maintained for patients of Asian, African/Caribbean, and Hispanic descent.2-5 Childhood-onset SLE is associated with a higher incidence of LN and more-severe disease than adult-onset SLE.9 Although a proteinuria level of 500 mg/d is suggested as a threshold for further investigations, taking into consideration physiological causes of low-level proteinuria and to avoid unnecessary kidney biopsies, it is important to note that the severity of proteinuria varies considerably in severe active nephritis and can appear relatively “insignificant” at times. A holistic assessment including clinical, urinary, and laboratory parameters, and repeated investigations to note the progression of abnormal findings over time, are important in informing clinical management decisions. Because clinical findings do not always correlate with the extent or
severity of kidney involvement,\textsuperscript{10, 11} a kidney biopsy is useful to confirm the diagnosis and for the assessment of activity and chronicity features that inform treatment decisions and prognosis.\textsuperscript{10-20} Kidney biopsies should be read by an experienced kidney pathologist and classified according to the ISN/RPS scheme.\textsuperscript{21-23} Electron microscopy, where available, is helpful in ascertaining ultrastructural details of histopathology such as the extent and severity of podocyte injury and the location of immune deposits. Clinicians should pay attention to the detailed description of both active and chronic histopathologic features affecting different elements of the kidney parenchyma, especially regarding potentially reversible active lesions versus chronic damage not reversible by immunosuppressive medications (Figure 2).

<table>
<thead>
<tr>
<th>Components of the activity index</th>
<th>Score</th>
<th>Calculating the activity score</th>
<th>Extent of lesion</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rendocapillary hypercellularity</td>
<td>0–3</td>
<td>Not present</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neutrophils and/or karyorrhexis</td>
<td>0–3</td>
<td>Present in &lt;25%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>(0–3)</td>
<td>Present in 25–50%</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hyaline deposits (wire loop and/or hyaline thrombi)</td>
<td>(0–3)</td>
<td>Present in &gt;50%</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cellular/fibrocellular crescents</td>
<td>0–3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial inflammation (interstitital leukocytes)</td>
<td>0–3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total:</strong> 0–24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Items included into the NIH chronicity score</th>
<th>Score</th>
<th>Calculating the chronicity score</th>
<th>Extent of lesion</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total glomerulosclerosis (global + segmental)</td>
<td>0–3</td>
<td>Present in &lt;10%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fibrous crescents</td>
<td>0–3</td>
<td>Present in 10–25%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>0–3</td>
<td>Present in 25–50%</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>0–3</td>
<td>Present in &gt;50%</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Total:</strong> 0–12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Other histologic findings not included in the activity or chronicity score**
- Foot process effacement (lupus podocytopathy)
- Collapsing lupus glomerulopathy
- Vascular lesions (arteriosclerosis, non-inflammatory vascular immune complex deposits, thrombotic microangiopathy, non-inflammatory necrotizing vasculitis, true renal vasculitis)

**Figure 2** | Activity and chronicity items included in lupus nephritis kidney biopsy report. NIH, National Institutes of Health, USA.

**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).

This recommendation places a relatively higher value on the various benefits associated with hydroxychloroquine use reported in observational studies (including lower rates of disease flares, progressive kidney damage, and vascular complications) and on the generally favorable safety profile.
of hydroxychloroquine treatment. It places a relatively lower value on the lack of large-scale prospective RCT data.

**Key information**

**Balance of benefits and harms**

The reported benefits of antimalarial use in SLE include lower flare (including kidney) rates, higher response rates to therapy, slower progression of kidney disease, lower incidence of cardiovascular (CV) and thrombotic events in patients with antiphospholipid antibodies, less organ damage, improved lipid profile, and better preservation of bone mass.

Hydroxychloroquine use in pregnancy has been associated with a decrease in lupus activity and a satisfactory safety profile in both the mother and the fetus. Significant side effects are uncommon but include skin rash, increase in skin pigmentation, muscle weakness, and visual change or loss of vision. Hydroxychloroquine may accumulate in lysosomes and cause a form of phospholipidosis with accumulation of multilamellar zebra bodies in podocytes that can mimic the appearance of Fabry disease.

**Certainty of evidence**

Moderate-certainty data support the benefit of hydroxychloroquine use in patients with SLE, but in LN, the available evidence is from observational studies and post hoc analyses. In a 24-week randomized controlled trial (RCT) that included 47 patients, the Canadian Hydroxychloroquine Study Group reported a higher incidence of SLE flares in patients who stopped hydroxychloroquine compared to those who continued treatment, with a hazard ratio (HR) of 2.50 (95% CI: 1.08–5.58). The frequency of severe LN flares was also increased but did not reach statistical significance. A systematic review that included 95 reports published between 1982 and 2007, 5 of which were RCTs, concluded that hydroxychloroquine use could prevent SLE flares and increase long-term patient survival, while toxicity was infrequent, mild, and usually reversible; and hydroxychloroquine use in pregnancy was associated with a decrease in lupus activity without harm to the fetus. Low-certainty observational studies have indicated that hydroxychloroquine may have kidney benefits, protective effects against infection, and may increase complete remission rate in patients with LN. Although the certainty of the evidence is low due to study limitations, indirectness, or imprecision, this is stated as a recommendation because of the relatively large effect sizes reported and the generally satisfactory safety data. Two observational studies reported an association between hydroxychloroquine treatment and reduced mortality in patients with LN, but the certainty of evidence for this outcome is very low.

**Values and preferences**

The potential benefits of preventing organ damage and vascular complications were judged as being important to patients. The Work Group also judged that the relatively low risk of adverse events associated with hydroxychloroquine would also be important to patients. Therefore, the Work Group felt that nearly all well-informed patients in the target population would choose to receive hydroxychloroquine treatment in comparison to no treatment.

**Resource use and costs**

Hydroxychloroquine can be an expensive drug in some countries. Therefore, in low-resource settings, it may be acceptable to substitute structurally similar drugs such as chloroquine that have a similar mechanism of action but are less expensive.
**Considerations for implementation**

Because of the risk of hemolysis in patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency, measurement of G6PD levels is preferred in men, especially those of African, Asian, or Middle Eastern origin, before starting hydroxychloroquine. However, this risk appeared low, according to the findings of a recent report.51 Updated guidelines from the Royal College of Ophthalmologists in United Kingdom published in 2020 do not recommend baseline examination prior to initiating treatment (https://www.rcophth.ac.uk/resources-listing/2609/), and yearly monitoring should begin after 1 year of therapy in patients with additional risk factors (concomitant tamoxifen use; estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m²; dose of hydroxychloroquine >5 mg/kg/d; use of chloroquine) or after 5 years of therapy otherwise.52 Nevertheless, recent data showed that hydroxychloroquine retinopathy in long-term users is more common than previously perceived, affecting 0.5% after 6 years of treatment, increasing to 7.5% of long-term users in general, and could be >20% when treatment duration is over 20 years. The recommended starting dose of hydroxychloroquine is around 5mg/kg/d (≤2.3 mg/kg/d for chloroquine). Doses of 2-3 mg/kg/d may not achieve adequate blood levels and could be associated with higher flare rates.53, 54 In patients with eGFR <30 ml/min per 1.73 m², the dose of hydroxychloroquine should be reduced by ≥25%. Also, antimalarials may rarely be cardiotoxic manifesting as cardiomyopathy or conduction abnormalities in patients with a high cumulative exposure.

**Rationale**

Data from multiple observational cohort studies show various benefits of hydroxychloroquine treatment in SLE, notably a reduced incidence of flare and organ damage accrual, and a relatively low rate of drug-related adverse effects, including ocular toxicity. Despite the relatively low-certainty evidence, the overall balance between benefits and potential risks provides the basis for recommending its use as part of general management in patients with SLE.
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 3.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Risk attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular risk</td>
<td>• Lifestyle modifications – smoking cessation, body weight optimization, exercise</td>
</tr>
<tr>
<td></td>
<td>• Dyslipidemia management</td>
</tr>
<tr>
<td></td>
<td>• Low-dose aspirin during pregnancy</td>
</tr>
<tr>
<td>Proteinuria (Chapter 1)</td>
<td>• Avoidance of high-sodium diet</td>
</tr>
<tr>
<td></td>
<td>• Blood pressure control</td>
</tr>
<tr>
<td></td>
<td>• RAS blockade</td>
</tr>
<tr>
<td>Infection risk</td>
<td>• Assess medical history of herpes zoster and tuberculosis</td>
</tr>
<tr>
<td></td>
<td>• Screening for HBV, HCV, HIV, and HBV vaccination</td>
</tr>
<tr>
<td></td>
<td>• <em>Pneumocystis jiroveci</em> prophylaxis (issue of potential adverse drug reaction discussed below)</td>
</tr>
<tr>
<td></td>
<td>• Influenza and pneumococcal vaccination</td>
</tr>
<tr>
<td></td>
<td>• Individualized consideration for recombinant zoster vaccine</td>
</tr>
<tr>
<td></td>
<td>• Individualized consideration for other infectious organisms as dictated by public health concerns at the time of treatment</td>
</tr>
<tr>
<td>Bone injury</td>
<td>• Bone mineral density and fracture risk assessment</td>
</tr>
<tr>
<td></td>
<td>• Calcium and vitamin D supplementation</td>
</tr>
<tr>
<td></td>
<td>• Bisphosphonates when appropriate</td>
</tr>
<tr>
<td>Ultraviolet light exposure</td>
<td>• Broad-spectrum sunscreen</td>
</tr>
<tr>
<td></td>
<td>• Limit ultraviolet light exposure</td>
</tr>
<tr>
<td>Premature ovarian failure</td>
<td>• Gonadotropin-releasing hormone agonists (i.e. leuprolide)</td>
</tr>
<tr>
<td></td>
<td>• Sperm/oocyte cryopreservation</td>
</tr>
<tr>
<td>Unplanned pregnancy</td>
<td>• Individual evaluation and counselling for contraception type (preference, thrombosis risk, age)</td>
</tr>
<tr>
<td>Cancer</td>
<td>• Evaluate individual risk factors for malignancies</td>
</tr>
<tr>
<td></td>
<td>• Age-specific malignancy screening</td>
</tr>
<tr>
<td></td>
<td>• Limit lifetime cyclophosphamide exposure to &lt;36 g</td>
</tr>
</tbody>
</table>

Figure 3 | Measures to minimize the risk of complications related to lupus nephritis or its treatment. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RAS, renin–angiotensin system.

Although many of the above recommendations also apply to patients with proteinuric kidney diseases treated with immunosuppression in general (KDIGO 2021 GD Guideline Chapter 1), some risks are especially relevant to patients with SLE and LN. Patients with SLE show increased mortality rates when compared to age- and sex-matched controls in the general population. Infections, CV complications, and CKD, especially kidney failure, are major causes of death. Early deaths are related to infections or lupus activity, while CV and malignant complications and deaths related to kidney failure account for late mortalities.
Cardiovascular complications in patients with LN

Patients with SLE have both traditional (dyslipidemia, smoking, obesity, etc.) and non-traditional (proteinuria, inflammation, etc.) CV risk factors. A patient often has multiple risk factors, which can be secondary to disease-related organ damage (especially CKD, hypertension, proteinuria) or treatment (such as glucocorticoids and calcineurin inhibitors [CNIs]). Regular evaluation of various risk factors and timely treatment are essential to prevent premature CV complications.59

Infections in patients with LN

Infection is a leading cause of death in patients with LN, and infection-related deaths are more common during the initial phase of management following exposure to intensive immunosuppressive therapy.49, 55, 60 There are data to suggest a higher incidence of adverse outcomes related to infections in Asia, which may be related to delayed presentation and the access to care.60 Avoidance of overimmunosuppression is an important measure to reduce the risk of infections and adverse outcomes. Prophylaxis for Pneumocystis is standard practice in organ transplant recipients, but its role in patients on high-dose glucocorticoid therapy without human immunodeficiency virus (HIV) infection remains controversial, and there are few data from patients with SLE.2, 61 Antibiotic-related adverse drug reactions are not infrequent in patients with lupus, and in an early survey, 31% reported allergy to sulfonamide, with one-fifth of these patients also reporting worsening of SLE with the drug intolerance.62 In a retrospective study from Thailand that included 132 patients with various connective tissue diseases, trimethoprim/sulfamethoxazole (TMP-SMX) was effective in preventing pneumocystis pneumonia, and adverse drug reaction occurred in only 9.4% of patients with SLE given prophylaxis.63 However, a recent retrospective study from Japan reported a drug allergy rate of 41.9% in patients with lupus given TMP-SMX prophylaxis with conventional dosing, but only 10.7% in those with gradual introduction of the drug over a 9-day period.64 Pneumocystis pneumonia is a serious complication in patients who are immunosuppressed and can result in fatality. Prophylaxis should be actively considered, taking into consideration a patient’s allergic diathesis and available alternatives. The rate of Herpes zoster is 2–10 times higher in patients with SLE than in healthy controls, but the role of antiviral prophylaxis is uncertain. Available zoster vaccine preparations include the live-attenuated vaccine Zostavax® and the adjuvanted recombinant vaccine Shingrix. In general, live vaccines should be avoided in immunosuppressed subjects. There are no data on the efficacy of the recombinant zoster vaccine in patients with lupus, and there is concern about whether the adjuvant might affect disease activity. There is also concern that the polio vaccination has been associated with lupus flares, whereas the data on influenza vaccination are conflicting. Response to vaccination is reduced following exposure to high-dose immunosuppression.65

Contraception and pregnancy

Pregnancy in patients with LN is associated with increased maternal complications and inferior fetal outcomes compared with the occurrence in healthy individuals, and the risks are higher when LN is active. Some of the frequently used medications in patients with lupus are contraindicated during pregnancy, such as mycophenolate mofetil (MMF), cyclophosphamide, and warfarin. Counseling with regard to contraception and pregnancy should be done early in patients of childbearing age. Patients should be seen by a gynecologist to discuss the choice of methods for contraception. For patients who prefer oral hormonal contraception, estrogen–progestin contraceptives with ethinyl estradiol dose at not higher than 30 μg may be used in patients who are negative for antiphospholipid antibodies and with stable low disease activity, whereas progestin-only contraceptives are preferable in patients with a moderate or high level of disease activity. Estrogen-containing contraceptives should be avoided in patients with antiphospholipid antibodies or a history of thrombosis, in view of the risk of thromboembolism.66 Data from women exposed to chemotherapy showed efficacy of gonadotrophin-releasing hormone (GnRH) analogues in reducing the rate of premature ovarian failure, whereas the
putative gonadal protective effect of oral contraceptive pills appeared variable. Fertility protection with GnRH agonists, or sperm and oocyte cryopreservation, should be considered in patients treated with cyclophosphamide, especially in patients with high cumulative exposure.

**Bone health**

Glucocorticoid therapy, especially when high doses are used for long durations, increases bone loss. In children, glucocorticoid cumulative dose affects peak bone mass and growth. Individual evaluation of fracture risk can be estimated using patient demographics and clinical history, glucocorticoid dose, and the Fracture Risk Assessment Tool (FRAX) score. Calcium (optimal intake 1000–1200 mg/d) and vitamin D supplementation are recommended for patients with LN, as well as consideration for oral bisphosphonates according to individual risk assessment.

**Malignancies in patients with LN**

Patients with SLE have increased risk of malignant tumors, including non-Hodgkin’s lymphoma, lung, liver, vulvar/vaginal, thyroid, nonmelanoma skin cancer, and the risk (especially with bladder cancer) is increased in patients with a history of exposure to cyclophosphamide. In general, the surveillance for malignancies in patients with LN follows the cancer-screening policies for the general population in the local community, and specific malignancy screening guidelines for patients with SLE are either lacking or largely opinion-based. Although there is preliminary evidence showing efficacy and safety of human papillomavirus vaccines in patients with SLE, there is also controversy about whether the vaccine may cause predisposition to the development of SLE or lupus-like disease.
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 4)

Figure 4 | Immunosuppressive treatment for patients with Class I or Class II lupus nephritis.

Patients with Class I or Class II LN generally have normal kidney function, or at most, low-grade proteinuria that is well below the nephrotic-range, and sometimes microscopic hematuria. For these patients, no specific immunosuppressive therapy beyond what is being given for nonrenal lupus is needed.80

Patients with Class I or II histology but with nephrotic-range proteinuria or NS are considered to have lupus podocytopathy. This diagnosis may be confirmed by demonstrating diffuse podocyte effacement on electron microscopy. Clinically and histologically, these patients are similar to those with minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), often showing a good response to glucocorticoid treatment.81-83 Although there have been no RCTs, observational data showed that over 90% of patients given glucocorticoid monotherapy achieved remission within a median time of 4 weeks.81, 84-88 Data on relapse are even more limited, but there appears to be a significant risk of relapse after glucocorticoids are tapered.89 Although optimal duration is not known, maintenance with low-dose glucocorticoid plus an additional agent such as mycophenolic acid analogues (MPAA), azathioprine, or a CNI is suggested, especially in patients with a history of relapse.

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 either one of the following:

i. mycophenolic acid analogues (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 (for example estimated glomerular filtration rate [eGFR] ≤45 ml/min per 1.73 m²) (1B).

This recommendation places a high value on results from clinical trials demonstrating that combined immunosuppressive regimens that include glucocorticoids and either low-dose intravenous cyclophosphamide or MPAA (dual immunosuppressive therapy), when given as initial treatment, improved kidney outcomes in patients with active severe LN. This recommendation also places a high value on results from recent clinical trials demonstrating that triple immunosuppressive regimens that include belimumab or voclosporin (or tacrolimus) added to the above dual immunosuppression were associated with enhanced clinical efficacy. In the case of CNI, the improved clinical response was driven by greater reduction of proteinuria compared with placebo, and in the case of belimumab, a reduced incidence rate of adverse kidney outcomes was also observed in post hoc analysis. Nevertheless, the Work Group acknowledges the variation between patients and the results from post hoc subgroup analyses suggesting that the enhancement of therapeutic efficacy associated with the addition of belimumab may not be applicable to all patients, and in particular, patients who are treated with cyclophosphamide concomitantly. Also, the Work Group emphasizes the importance of preventing potential adverse effects that could result from the use of CNIs and cautions the use of this group of medications in patients with severely compromised kidney function, as patients with CKD G3b or above were excluded from the respective clinical trials. A summary of recommended options of initial therapy for active proliferative LN is shown in Figure 5.
Figure 5 | Recommended approach for initial therapy of active Class III/IV lupus nephritis.

Caution is warranted when CNI is used in patients with significantly impaired kidney function, in view of increased susceptibility for severe consequences due to CNI nephrotoxicity. The eGFR and serum creatinine levels stated in the figure were patient selection criteria adopted in the respective clinical trials. †Refer to Figure 6 for examples of corticosteroid treatment regimen. ‡Refer to Figure 9 for durations of CNI or belimumab treatment in clinical trials. §Refer to Figure 7 for comments on cyclophosphamide regimens. b.i.d., twice daily. CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil; p.o., oral; q2wk, every 2 weeks; q4wk, every 4 weeks; s.c., subcutaneous; SCr, serum creatinine.

Key information

Balance of benefits and harms

The short-term prognosis of patients with proliferative LN improved dramatically when treatment with high-dose glucocorticoids was started in the 1960s.90 However, the long-term kidney prognosis continued to be poor as many patients progressed to kidney failure despite treatment. In landmark studies during the 1980s, the addition of cyclophosphamide to glucocorticoids was shown to be superior to treatment with glucocorticoids alone in preserving long-term kidney survival in active severe LN.13,
Dual immunosuppressive regimens comprising glucocorticoids and cyclophosphamide were standard-of-care initial therapy for active proliferative LN for decades. But the significant incidence of adverse effects, due to the high glucocorticoid dose and the toxicities of cyclophosphamide, prompted investigation of alternative induction regimens.

Subsequent investigations aiming to improve the risk–benefit ratio of treatment, in a study of 90 patients of European descent with active LN, showed that, when compared to standard high-dose cyclophosphamide, a reduced-dose cyclophosphamide regimen was associated with no statistically significant difference in efficacy both short- and long-term and an improved side-effect profile. In a short-term trial that included 100 patients from India, reduced-dose cyclophosphamide showed similar efficacy as MPAA when both were combined with glucocorticoids. In view of the scarcity of data on reduced-dose cyclophosphamide in patients of African or Hispanic descent, there is concern as to whether this regimen is effective in these patient groups. Figure 7 shows the details of cyclophosphamide-dosing regimens.

Following its established efficacy in preventing organ transplant rejection, MPAA was investigated in LN and was shown to have efficacy similar to that of cyclophosphamide in treating active LN. The dose is typically MMF 2–3 g/d (or equivalent for MPAA). The rate of adverse events in patients treated with glucocorticoids and MPAA appeared not significantly reduced compared with cyclophosphamide in clinical trials with MMF dose of 3 g/d, suggesting a dose effect and possible racial or ethnic variation in tolerability to MPAA. Also, concomitant high-dose glucocorticoids contributed to many treatment-associated adverse events. Based on generally favorable real-world clinical experience, combined immunosuppression with glucocorticoids and MPAA is widely used as initial treatment of proliferative LN.

CNIs reduce IL-2 transcription and T lymphocyte proliferation and have a direct modulatory effect on podocyte cytoskeleton thereby reducing proteinuria due to podocyte injury. The addition of fixed-dose tacrolimus to low-dose MPAA and glucocorticoids in a triple immunosuppressive regimen (termed “multitargeted therapy”) was investigated in Chinese patients. A prospective study including 40 LN (IV+/-V) patients from China demonstrated higher 24-week response rates in patients treated with the “multitarget” regimen compared with standard-dose cyclophosphamide and glucocorticoids. These findings were later corroborated in a trial of 368 Chinese patients with active LN and baseline serum creatinine ≤3 mg/dl (265 μmol/l; translating to eGFR level of around 25 ml/min per 1.73 m²), showing a higher complete response rate at 6 months in the triple immunosuppressive scheme than cyclophosphamide, though with numerically higher numbers of adverse events. Yet, continued follow-up data showed similar cumulative response rates at 24 months between patients who continued triple therapy and controls treated with sequential cyclophosphamide induction followed by azathioprine maintenance.

A triple immunosuppressive regimen of voclosporin added to standard-dose MPAA and a rapid-tapering regimen of glucocorticoids was tested in phase 2 (Aurinia Urinary Protein Reduction Active-Lupus with Voclosporin [AURA-LV]) and phase 3 (Aurinia Renal Response in Active Lupus with Voclosporin [AURORA 1]) multinational studies that included patients with baseline eGFR >45 ml/min per 1.73 m². The response rates at 24 and 52 weeks, respectively, were higher in voclosporin treated groups compared with placebo, while all patients received MPAA plus rapid-tapering glucocorticoids. An excessive number of severe adverse events including deaths was noted in voclosporin-treated patients only in the phase 2 trial and was thought to be a center effect. Pooled phase 2 and phase 3 data showed no statistically significant difference in the incidence of adverse events. Patients who completed the phase 3 trial were eligible to continue on the same blinded therapy in a 2-year continuation study (AURORA 2; 116 of 179 patients in the voclosporin arm and 100 of 178 patients in the control arm). Results from the completed AURORA 2 Continuation Study showed sustained reduction of proteinuria with voclosporin treatment, and stable kidney function in both groups, with no safety signal. Improved treatment response rate in patients treated with CNIs was
mainly driven by earlier and more effective suppression of proteinuria, while the follow-up data to date showed similar kidney function in the CNI-treated group versus controls. The impact of the addition of a CNI on long-term kidney survival remains unclear.

Abnormal B lymphocyte hyperreactivity is a characteristic feature in the pathogenesis of SLE. B-cell activating factor (BAFF, also known as B lymphocyte stimulator BLyS) is a cytokine expressed in B cell lineage cells and acts as a potent B cell activator. Belimumab, a human monoclonal antibody that inhibits BAFF, was approved by United States (U.S.) Food and Drug Administration (FDA) for the treatment of SLE in 2011 based on efficacy demonstrated in clinical trials. The addition of belimumab to glucocorticoids plus either standard-dose MPAA or low-dose cyclophosphamide followed by azathioprine in a triple immunosuppressive regimen was evaluated in a multinational Phase 3 trial (Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis [BLISS-LN]) of 448 patients observed over 104 weeks. Patients treated with belimumab had superior primary efficacy renal response rate (PERR, a composite end-point with proteinuria ≤0.7 mg/g) compared to placebo, while all patients received standard dual immunosuppression. The 2 groups showed similar rates of adverse events. Results from secondary analysis and open-label extension study of 28 weeks showed that the efficacy advantage was maintained, and patients treated with the belimumab-containing triple immunosuppressive regimen had lower rates of adverse kidney outcomes. While intravenous belimumab was used in the BLISS-LN trial, the U.S. FDA approved both the intravenous (i.v.) and subcutaneous (s.c.) routes of belimumab treatment for LN in December 2020, the latter based on pharmacokinetics matching which showed similar exposure between the 2 administration routes with higher trough level when given subcutaneously.

It is important to note that, while there was long-term data from controlled trials showing that cyclophosphamide combined with glucocorticoids as initial therapy for active LN was more efficacious than glucocorticoids alone in preserving kidney function, long-term data is relatively scarce for the other regimens, especially for the more recent treatments such as CNI and belimumab. In this regard, data from observational studies suggested that higher rates of response to induction therapy may translate into better long-term kidney survival, but the data were from treatment regimens that did not include a CNI.

In summary, Class III and Class IV LN are severe diseases that results in acute kidney injury that leads to permanent nephron loss if not treated promptly with effective therapeutic regimens. Severe LN is an important, but treatable, cause of patient morbidity and mortality in many parts of the world. Advances in therapy have resulted in increased efficacy and reduced incidence of adverse events, the latter could be due to disease or the toxicities of treatments. Attempts to reduce medication side-effects, especially those due to glucocorticoids and cyclophosphamide, have been modestly successful. Despite the potential of important treatment-associated toxicities, the benefits of treating proliferative LN clearly outweigh the potential harms.

Certainty of evidence

In the 6 RCTs that compared i.v. cyclophosphamide with glucocorticoids, there was moderate certainty of evidence for a kidney benefit and decrease in kidney relapse. The certainty of the evidence from these RCTs was downgraded to moderate because of study limitations (unclear blinding of participants and personnel, unclear allocation concealment; Supplementary Table S5). High-dose versus low-dose cyclophosphamide has been compared in a few RCTs (Supplementary Table S6). The results from these trials indicate that low-dose cyclophosphamide is associated with fewer adverse events (such as infection, malignancy, leukopenia, and bone toxicity, although in some studies, the efficacy also appeared lower than that of the high-dose regimen), with moderate
certainty of the evidence because of serious imprecision (only a few events, resulting in wide confidence intervals [CIs] indicating appreciable benefit and harm).

From the RCTs, there is moderate certainty in the evidence that MMF exhibits a similar efficacy, and a different side-effect profile compared with i.v. cyclophosphamide. The certainty of the evidence was downgraded to moderate because of unclear reporting of allocation concealment in trials (Supplementary Table S7\textsuperscript{12}, 96-98, 116, 120-123).

There is low certainty evidence that triple immunosuppressive regimens that include tacrolimus, reduced-dose MPAA, and glucocorticoids is superior to standard-of-care regimens when used as initial therapy, with similar incidence of adverse events (Supplementary Table S8\textsuperscript{15}, 99, 100, 116). There is high certainty evidence showing that triple therapy with voclosporin, standard-dose MPAA, and rapid-tapering glucocorticoids is superior to MPAA and rapid-tapering glucocorticoids in achieving renal response (mainly driven by more effective suppression of proteinuria) with similar incidence of adverse events (Supplementary Table S9\textsuperscript{103}, 104, 124 and Supplementary Table S10\textsuperscript{19}, 99, 100, 103, 104). The long-term effect of CNI-containing immunosuppressive regimens in LN on preservation of kidney function (≥50% loss of GFR or kidney failure) still needs to be demonstrated (Supplementary Table S10\textsuperscript{19}, 99, 100, 103, 104).

There is moderate-to-high certainty evidence showing that adding belimumab to MPAA or reduced-dose cyclophosphamide and glucocorticoids results in higher renal response rates with similar incidence of adverse events compared with placebo, and low certainty evidence for an effect of belimumab in renal relapse prevention and reduction of adverse kidney outcomes (Supplementary Table S11\textsuperscript{107}, 109, 125).

**Values and preferences**

Without treatment, the prognosis for kidney survival in patients with proliferative LN is poor, so the Work Group judged that most well-informed patients with Class III and IV LN would choose to be treated with one of the immunosuppression regimens outlined previously. Given the risks of infertility associated with cyclophosphamide and the spectra of future malignancy, most patients of childbearing age who anticipate conceiving in the future, and most patients, in general, will likely opt for initial MPAA- over cyclophosphamide-based treatment. Low-dose i.v. cyclophosphamide has less risk than standard-dose and is a reasonable alternative to MPAA, but because the data favoring low-dose cyclophosphamide have largely come from White patients with mild to moderately severe LN, this alternative may not be appropriate for the treatment of severe LN in patients of African or Hispanic ancestry.

Triple immunosuppressive regimens that include a CNI, together with MPAA and glucocorticoids, may be particularly useful for patients with high-grade proteinuria associated with extensive podocyte injury. Caution is recommended with the use of this regimen in patients with impaired kidney function and/or significant chronic damage in kidney biopsy. In the voclosporin trials, patients with baseline eGFR at or below 45 ml/min per 1.73 m\textsuperscript{2} were excluded, and this eGFR threshold is also included in the regulatory approval for the drug. In the clinical trial on Chinese patients with the “multitarget” regimen that included fixed-dose tacrolimus, reduced-dose MPAA and glucocorticoids, patients were continued on this regimen for up to 2 years. The primary endpoint in the phase 3 voclosporin trial was assessed at 1-year, and results from a further 2-year extension on the same blinded treatment showed sustained reduction of proteinuria and stable kidney function during follow-up, with no increase in adverse events compared with controls.\textsuperscript{106} The optimal duration of CNI treatment for LN remains uncertain, and there is insufficient data on subsequent tapering or discontinuation, or clinical outcomes thereafter.

In addition to increasing the therapeutic response rate, post hoc analysis showed that adding belimumab to MPAA or cyclophosphamide and glucocorticoids may confer further benefits of reducing
renal relapses and the rate of adverse kidney outcomes, and eGFR value was numerically higher in patients treated with belimumab compared with placebo. Post hoc analysis showed that the efficacy benefit in LN associated with belimumab treatment was driven by patients with baseline urine protein/creatinine ratio (PCR) <3g/g.\textsuperscript{109} Whether this could be related to the increased clearance of belimumab in patients with heavy proteinuria remains to be investigated. Results from an independent analysis of the BLISS-LN data by U.S. FDA also showed that the efficacy of belimumab was driven by patients with lower levels of proteinuria at baseline, but post hoc time-to-event analysis of the high proteinuria group (\textgtr等于3 g/g) suggested that the estimated risk of a kidney-related event or death was lower in the belimumab group.\textsuperscript{126} Results from the 28-week open-label extension of the BLISS-LN study showed continued increase in the proportions of patients achieving primary efficacy renal response or complete renal response, and no safety signal, associated with belimumab treatment.\textsuperscript{108}

Despite these being post hoc analysis or extension study results, the Work Group attributes value to these observations, which are relevant to optimizing the choice of therapies to match different patient characteristics.

\textbf{Resource use and costs}

Management of active LN with immunosuppression is resource and labor intensive because the medications and the surveillance for potential complications are costly. Intravenous administration requires an infusion center with supervision, and patients must be monitored frequently for treatment- or disease-related complications and require frequent clinical laboratory testing. However, it is likely that these costs are less over time than those associated with managing CKD and kidney failure resulting from no treatment, although a direct economic analysis has not been done. Furthermore, there have been no comparisons of quality of life between patients with CKD, patients with kidney failure receiving kidney replacement therapy, and patients receiving immunosuppression, especially with high-dose or prolonged administration of glucocorticoids. MPAA regimens were associated with higher medication costs but lower facility costs and a superior quality of life compared to i.v.
cyclophosphamide regimens.\textsuperscript{127-129}

Addition of a third drug (CNI or belimumab) increases the costs of therapy,\textsuperscript{130} while the potential increase in complete response rates and prevention of renal relapses may be cost-saving.\textsuperscript{131} Access to treatment, cost barrier, and cost of additional monitoring such as blood level measurements are additional factors to consider. This Work Group advocates individualized choice of treatment regimen, including informed discussions with patients, to suit unique patient characteristics.

\textbf{Considerations for implementation}

In view of the significant treatment costs,\textsuperscript{129, 132, 133} the choice of therapy is often region-specific and depends on drug availability, reimbursement policies, and the financial means of individual patients. Other considerations when choosing initial therapy for LN include likelihood of adherence, age, prior immunosuppressive exposure, disease tempo and severity, and race and ethnicity.

Physicians may choose an i.v. regimen if suboptimal adherence is anticipated. Age is an important factor with respect to preservation of fertility, as susceptibility to gonadal failure after cyclophosphamide use increases with age. Susceptibility to future malignancies increases with higher lifetime cyclophosphamide exposure, so a detailed knowledge of prior therapies is important. Despite these considerations for cyclophosphamide, many physicians would initially choose standard-dose cyclophosphamide for patients in whom kidney function is rapidly deteriorating and whose biopsy shows severe activity (e.g., capillary necrosis, an abundance of crescents). It should be noted that there
are sparse data on this group of patients who present with aggressive disease, as their clinical characteristics precluded them from inclusion in clinical trials. Physicians caring for patients of mixed ethnic background or Hispanic ethnicity may choose MPAA over cyclophosphamide as there are some post hoc analysis data suggesting it has higher efficacy, whereas physicians caring for Chinese patients may want to choose MPAA and glucocorticoids, or triple immunosuppression with glucocorticoids plus low-dose MPAA plus low-dose CNI, as opposed to a cyclophosphamide-based regimen.

Based on benefit versus risk considerations, the inclusion of CNI in the treatment regimen may be preferred in patients with high-level proteinuria due to podocyte injury and without significantly impaired kidney function, while the inclusion of belimumab may be preferred in patients treated with MPAA in contrast to cyclophosphamide, and when prevention of disease flares and adverse kidney outcomes assumes high priority such as in patients with significant CKD. Extra caution must be exercised when using CNI in patients with severely impaired kidney function, with considerations of the balance between potential benefit versus harm. In a trial investigating the triple immunosuppressive regimen of glucocorticoids and reduced-dose MMF and fixed-dose tacrolimus in Chinese patients, patients with baseline serum creatinine $>$3 mg/dl (265 μmol/l) were excluded, and the voclosporin trials excluded patients with baseline eGFR $\leq$45 ml/min per 1.73 m$^2$. The overall results suggest that kidney function remained relatively stable when voclosporin or tacrolimus was used at the reported doses for 2-3 years. Also, results from voclosporin trials suggest that inclusion of a CNI might facilitate rapid glucocorticoid tapering. In addition, results from post hoc analysis suggested that belimumab might not be as effective in patients who present with heavy proteinuria in the nephrotic range.

With regard to the duration of treatment, reduced-dose cyclophosphamide is given for 12 weeks while standard-dose cyclophosphamide normally given for up to 6 months, and MPAA can be continued after the early treatment phase as maintenance immunosuppression. CNIs can be used as long-term maintenance immunosuppression, but vigilance to prevent nephrotoxicity is warranted. Results from the 2-year continuation study (AURORA 2) suggested safety of voclosporin treatment for 3 years in patients with LN patients whose baseline eGFR was $>45$ ml/min per 1.73 m$^2$. Results from the BLISS-LN open-label extension study suggested safety of continuing belimumab treatment for around 2.5 years.

**Rationale**

Class III or IV LN is an aggressive disease that requires prompt and effective therapy to abate ongoing injury and destruction of normal nephrons. Immunosuppressive treatment targets the active inflammatory lesions in kidney histopathology, in contrast to the chronic lesions, the extent of which portend CKD and long-term kidney prognosis.

The choice of initial treatment for Class III or IV LN entails personalized consideration of the balance between benefit and risk and is informed by data on short-term response and long-term efficacy and safety, potential adverse effects including infections and cumulative toxicities, quality of life, and factors relevant to patient experience and adherence.

Patient and kidney survival rates in Class III or Class IV LN have improved since the 1970s, first with the use of glucocorticoids, and subsequently following the adoption of combined immunosuppressive regimens with cyclophosphamide or MPAA ± CNI or belimumab as standard therapy.

Glucocorticoids remain an integral component in initial therapy for Class III or IV LN based on their anti-inflammatory and immunosuppressive actions. The addition of the other immunosuppressants was
associated with lower relapse rates and improved long-term kidney survival compared with glucocorticoid treatment alone. Combined immunosuppressive regimens also facilitate glucocorticoid minimization, thereby reducing their adverse effects (Figure 6).

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 6).

<table>
<thead>
<tr>
<th>Methylprednisolone intravenous pulses</th>
<th>Standard-dose scheme</th>
<th>Moderate-dose scheme</th>
<th>Reduced-dose scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null or 0.25–0.5 g/day up to 3 days as initial treatment</td>
<td>0.25–0.5 g/day up to 3 days often included as initial treatment</td>
<td>0.25–0.5 g/day up to 3 days usually included as initial treatment</td>
<td></td>
</tr>
<tr>
<td>Oral prednisone equivalent (mg/day)</td>
<td>0.8–1.0 mg/kg (max 80 mg)</td>
<td>0.6–0.7 mg/kg (max 50 mg)</td>
<td>0.5–0.6 mg/kg (max 40 mg)</td>
</tr>
<tr>
<td>Week 0–2</td>
<td>60 mg</td>
<td>50 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Week 3–4</td>
<td>30 mg</td>
<td>25 mg</td>
<td>20 mg</td>
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<tr>
<td>Week 5–6</td>
<td>20 mg</td>
<td>15 mg</td>
<td>10 mg</td>
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<tr>
<td>Week 7–8</td>
<td>15 mg</td>
<td>10 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Week 9–10</td>
<td>12.5 mg</td>
<td>7.5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Week 11–12</td>
<td>10 mg</td>
<td>7.5 mg</td>
<td>5 mg</td>
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<tr>
<td>Week 13–14</td>
<td>5 mg</td>
<td>7.5 mg</td>
<td>&lt;5 mg</td>
</tr>
<tr>
<td>Week 15–16</td>
<td>&lt;5 mg</td>
<td>&lt;5 mg</td>
<td>&lt;2.5 mg</td>
</tr>
</tbody>
</table>

Figure 6 | Example of glucocorticoid regimens for lupus nephritis.

Glucocorticoids are used in all current treatment regimens of LN. These drugs have both immunosuppressive and anti-inflammatory effects and provide immediate treatment for the often extensive intrarenal inflammation that is seen in patients with Class III and Class IV LN. This regimen is necessary because there is a lag before the immunosuppressive effects of cyclophosphamide, MPAA, CNIs, or B cell–directed therapies are seen. The dose, tapering regimen, and duration of glucocorticoid schemes vary considerably among clinicians and are largely opinion-based. Examples are given in Figure 6.

The role of i.v. methylprednisolone pulses at the start of treatment is not well-studied but is commonly given as up to 3 daily doses of 500 mg each (range 250–1000 mg/d), especially in patients who present with a clinical syndrome of rapidly progressive glomerulonephritis (RPGN)—acute and severe deterioration of kidney function often accompanied by a high proportion of crescents or vascular lesions in the kidney biopsy, or when there are severe extrarenal manifestations, such as central nervous system or lung involvement.

To minimize the side effects due to high cumulative exposure to glucocorticoids, there is increasing use of initial i.v. glucocorticoid pulses followed by a lower starting dose and/or more-rapid taper of oral glucocorticoid in recent clinical trials. Results from a retrospective propensity analysis of data from 63 patients enrolled in the Aspreva Lupus Management Study (ALMS) and the phase 2 AURA-LV trial suggested that doses of glucocorticoids and MPAA lower than those adopted in ALMS may result in better long-term safety, including a reduction in lymphoproliferative disorders, skin cancers, and glucocorticoid-related side effects. In children, the avoidance of excessive glucocorticoid exposure also has implications for growth, psychosocial issues, and drug adherence. With accumulating data on the efficacy and glucocorticoid-sparing role of immunosuppressive medications such as
cyclophosphamide, MPAA, and triple immunosuppressive drug combinations, there is a move toward reducing exposure to glucocorticoids (Supplementary Table S1). Examples of dosing and tapering regimens in initial treatment of LN, based on published literature and recent clinical trials that investigate the efficacy and safety of new therapeutic agents, are shown in Figure 6. They serve to illustrate variations in exposure to glucocorticoids, but it is premature to recommend one over the other, as the evidence supporting these regimens is low as they have only been compared in relatively small clinical trials and observational studies. The use of reduced-dose glucocorticoids may decrease the incidence of major infections.

**Practice Point 10.2.3.1.2:** Intravenous cyclophosphamide should 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.

Cyclophosphamide may be given orally or intravenously, and in a standard-dose (also known as the modified National Institutes of Health (NIH) regimen or high-dose regimen) or low-dose (also known as the Euro-Lupus regimen). The dosing and duration for these regimens are given in Figure 7.

<table>
<thead>
<tr>
<th>Intravenous cyclophosphamide – modified (NIH regimen)</th>
<th>Intravenous cyclophosphamide (Euro-Lupus regimen)</th>
<th>Oral cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.v. 0.5–1 g/m² monthly for 6 months</td>
<td>i.v. 500 mg every 2 weeks for 3 months</td>
<td>p.o. 1.0–1.5 mg/kg/d (max 150 mg/d) for 2–6 months</td>
</tr>
<tr>
<td>Comments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy data included patients of different races/ethnicities</td>
<td>Efficacy data mainly in Caucasian patients, with some data from patients of Afro/Caribbean descent, Hispanic descent, Indian patients, and other Asian countries</td>
<td>Efficacy data included patients of different races/ethnicities</td>
</tr>
</tbody>
</table>

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

The choice of which regimen to use depends on several factors and can be individualized:

- **Efficacy:** Oral and standard-dose i.v. cyclophosphamide regimens have been used in diverse ethnic populations and for all levels of disease severity, and show equivalent efficacy. Reduced-dose cyclophosphamide (Euro-Lupus regimen) shows equivalent efficacy to standard-dose cyclophosphamide but was tested mainly in White patients. Emerging data suggest low-dose cyclophosphamide is effective in Asians, Hispanics, and Black patients, but these studies did not make direct comparisons to standard-dose i.v. cyclophosphamide (Supplementary Table S6).

- **Cost:** Intravenous cyclophosphamide is more expensive than oral and requires the availability of an infusion suite and experienced staff.

- **Convenience:** Oral cyclophosphamide does not require patients to stop work or family activities.

- **Toxicity:** The toxicities of cyclophosphamide may be considered immediate (e.g., gastrointestinal, susceptibility to infection) or delayed (e.g., loss of fertility, future malignancies).
Standard-dose i.v. cyclophosphamide was shown to be less toxic than oral cyclophosphamide, but the dose and duration of oral treatment in these reports were substantially higher and longer than those currently recommended (Supplementary Table S1313,148). The incidence of bladder toxicity is also felt to be lower with i.v. cyclophosphamide. Reduced-dose i.v. cyclophosphamide has the most favorable immediate toxicity profile among the 3 cyclophosphamide regimens.

The risk of future hematologic malignancy is related to total lifetime exposure (>36 g), as is myelofibrosis (>80 g). Total lifetime exposure plus age constitutes a significant risk factor for premature ovarian failure (>7.5–15 g/m² for young to older pediatric patients, respectively; 300 mg/kg for adults).

**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, patients who have a moderate to high prior cyclophosphamide exposure.**

Trials of MMF for initial treatment of proliferative LN have targeted dosing of 2–3 g/d. Several studies have shown that MMF has comparable short-term efficacy to oral or i.v. cyclophosphamide for induction of complete and partial renal responses (Supplementary Table S713-15, 98, 116, 120-123). MMF has significant gastrointestinal toxicity, and at moderate-to-high doses, some patients may not tolerate it. In patients with gastrointestinal intolerance, a trial of enteric-coated mycophenolic acid (MPA) in a dose range of 1440–2160 mg is warranted, in view of its greater gastrointestinal tolerance.141

Although MPAA does not predispose patients to gonadal failure or hematologic malignancies as does cyclophosphamide, the ALMS trial (target dose 3 g/d) showed a similar incidence of side effects between patients treated with MMF plus glucocorticoids and patients treated with cyclophosphamide plus glucocorticoids.12 In this trial, 9 deaths occurred in the MMF group, and 5 in the cyclophosphamide group. Seven of the 9 deaths in the MMF group were due to infections, and 7 of the 9 deaths in MMF-treated patients occurred in Asia. Concomitant high-dose glucocorticoids and the relatively high MPA exposure have been proposed as contributory factors to the higher-than-expected infection-related adverse outcomes in this trial. In this regard, data from kidney transplant clinical trials showed that, compared with an MMF dose of 2 g/d, an increased MMF dose of 3 g/d did not result in a higher efficacy in the non-Black patient population, but was associated with more adverse events.149 Therefore, consideration of the race or ethnicity of a patient, or the geographic locality, may also be relevant when deciding on the dose of MPAA to be used, in view of the potential differences in risk profiles among patients.

MPA pharmacokinetics varies considerably among patients, especially in the context of hypoalbuminemia and impaired kidney function. Data from small-scale studies suggested that an MPA area under the concentration-versus-time curve of 35–45 mg/hr/l or a trough level of 3.0–4.5 mg/l may serve to ensure adequate exposure during initial therapy, but the role of therapeutic drug-level monitoring remains to be established.150-154

MMF has been tested successfully in diverse ethnic groups. A more granular look at the efficacy of MMF in specific ethnic groups was done through a post hoc analysis of data from the ALMS study, the largest trial comparing MMF to i.v. cyclophosphamide to date.12,134 The analysis showed higher treatment response rates for MMF compared to cyclophosphamide in Hispanic patients (60.9% vs. 38.8%, $P = 0.011$) and patients from Latin America (60.7% vs. 32%, $P = 0.003$), whereas the response to MMF was numerically higher but not statistically different than that to cyclophosphamide in Black patients (53.9% vs. 40.0%, $P = 0.39$). A higher response rate to MMF than to cyclophosphamide in Hispanic patients was also reported in cohort studies.135 In contrast, the response rate to
cyclophosphamide was numerically higher but not statistically different than that to MMF in Asian patients (63.9% vs. 53.2%, \( P = 0.24 \)). Notwithstanding these results, both MPAA and cyclophosphamide are effective therapies for active LN.

Cyclophosphamide has historically been the first-choice treatment for very severe proliferative LN. An analysis of pooled data from various clinical trials of patients with Class III/IV LN, crescents in >15% of glomeruli, and abnormal serum creatinine (SCr) level at presentation showed a comparable early response to glucocorticoids plus either cyclophosphamide or MMF. However, the analysis also suggested that initial treatment with cyclophosphamide might be associated with a more sustained response and more favorable long-term kidney outcome than initial treatment with MMF. In the maintenance phase of ALMS, although not statistically different, patients initially treated with cyclophosphamide had numerically lower rates of disease flare compared with those initially treated with MMF.

**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.

CNI are potent immunosuppressive medications due to their inhibition of T lymphocyte activation and release of interleukin-2. They also modulate the podocyte cytoskeleton, leading to reduction of proteinuria in various glomerular diseases. The use of a CNI in the treatment of LN may therefore lead to more effective or more rapid reduction of proteinuria.

Data from short-term studies with follow-up of 6–12 months suggest that a regimen of glucocorticoids combined with cyclosporine or tacrolimus, with or without reduced-dose MPAA, as initial LN therapy has comparable efficacy to glucocorticoids combined with cyclophosphamide. Until recently, most of these trials had been done in Asia (see Practice Point 10.2.3.1.5). The largest trial, conducted in China, combined a fixed, relatively low-dose of tacrolimus (4 mg/d, achieved trough levels of 5.2–5.5 ng/ml [6.4–6.8 nmol/l]) with low-dose MMF (1 g/d) in patients with a baseline SCr level ≤3.0 mg/dl (265 μmol/l), and reported earlier attainment of renal response than in controls treated with the NIH-cyclophosphamide regimen with a higher complete renal response rate (46% vs. 26%) after 24 weeks of treatment. Extended follow-up, however, showed comparable renal response rates in both groups during the second year of treatment. Similarly, a study from Japan reported a complete response rate of 80% after 6 months of treatment with a triple immunosuppressive regimen that included glucocorticoids, reduced-dose cyclophosphamide, and tacrolimus.

The evidence from the few RCTs that compared triple-therapy to cyclophosphamide is judged as low certainty because of study limitations and indirectness (Supplementary Table S8). As these early trials mainly included patients of Asian ethnicity, and some excluded patients with severe disease, the generalizability of this therapy to the broader LN population is unclear (see also Practice Point 10.2.3.1.5).

Of importance, in the large Chinese study, the number of infections was higher in patients who received triple therapy than in those who were treated with cyclophosphamide, although this difference did not reach statistical significance. More data are also required on the incidence of acute and chronic CNI nephrotoxicity, the metabolic side effects of CNIs and their effect on blood pressure control, as well as the optimal duration of treatment and whether there may be a rebound of proteinuria after stopping CNI.

Voclosporin is an analogue of cyclosporine that exhibits enhanced potency in calcineurin inhibition. Voclosporin was noninferior to tacrolimus in the prevention of biopsy-proven acute rejection in a 6-
month multicenter open-label phase 2b trial that involved 334 low-risk kidney transplant recipients.\textsuperscript{158} Voclosporin for the treatment of active biopsy-proven Class III, IV, or V lupus nephritis was investigated in the AURA-LV trial,\textsuperscript{103} a phase 2 RCT of 265 subjects and the AURORA 1 trial,\textsuperscript{104, 159} a phase 3 RCT of 357 subjects. Both trials included patients of diverse ancestry. Voclosporin was compared to placebo, and all patients received glucocorticoids and MMF (target dose: 2 g/d) as background therapy. The rapidly tapered corticosteroid regimen used was novel. All patients received 2 doses of intravenous methylprednisolone (500 mg/dose) followed by 20–25 mg prednisone that was rapidly tapered to 2.5 mg/d by 16 weeks. The primary endpoint of these trials was renal response (RR), defined as urine PCR $\leq 0.5$ mg/mg, eGFR $\geq 60$ ml/min per 1.73m$^2$, or no decline of $>20\%$ from baseline, and prednisone dose of $<10$ mg/d for the 8 weeks prior to endpoint measurement.

In AURA-LV, 33\% of patients treated with voclosporin 23.7 mg twice per day reached an RR at 24 weeks compared to 19\% of placebo-treated patients (OR 2.03, $P < 0.05$).\textsuperscript{103} Similarly, in AURORA, 41\% of voclosporin-treated patients achieved RR at 52 weeks, compared to 23\% of placebo-treated patients (OR 2.65, $P < 0.001$).\textsuperscript{104, 159} A pooled analysis of the 2 trials showed that patients treated with voclosporin added to standard therapy had an RR rate of 44\% at 1 year, compared to 23\% in placebo patients ($P < 0.0001$).\textsuperscript{160} Adverse events were similar between the placebo and voclosporin arms.

Compared to other CNIs, such as cyclosporine and tacrolimus, voclosporin has a more consistent pharmacokinetic–pharmacodynamic relationship due to enhanced binding of the voclosporin–cyclophilin complex to calcineurin and reduced drug and metabolite load. Preliminary evidence, based on data from the AURA-LV and AURORA trials, suggests that therapeutic drug monitoring may not be necessary in patients.\textsuperscript{161}

Results from these 2 pivotal trials led to the U.S. FDA approval of voclosporin to treat adult patients with LN in January 2021. Of note, voclosporin is not recommended for patients with a baseline eGFR $\leq 45$ ml/min per 1.73 m$^2$, as these patients were excluded from the trials. Also, voclosporin has not been studied when given together with cyclophosphamide.

The positive results of AURA-LV and AURORA coupled with the Asian studies of tacrolimus and cyclosporine suggest triple immunosuppressive therapy incorporating a CNI can be an effective treatment regimen for LN. An advantage of a CNI-based regimen is the more rapid reduction of proteinuria. However, outstanding issues on the duration of the CNI, its tapering and suspension, and the long-term efficacy and safety of CNI triple therapy regimens remain under study.

A dual immunosuppressive regimen that included tacrolimus and glucocorticoids was compared with MPAA and glucocorticoids in a study conducted in Hong Kong. One hundred fifty patients were randomized to tacrolimus (target trough level $>5$ ng/ml) or MPAA plus glucocorticoids, and complete response rates at 6 months were similar in the tacrolimus and MPAA groups (62\% vs 59\%), while the profile of adverse events was different, with higher herpes zoster infections in MPAA-treated patients (18\% vs 3\%).\textsuperscript{162} This study also showed a high incidence of renal relapses when these induction agents were discontinued after 6 months and substituted with azathioprine for maintenance. A statistically nonsignificant trend of more disease flares and kidney function decline was suggested in patients treated with tacrolimus during induction phase. The evidence for efficacy for this trial is considered low-to-very low certainty (Supplementary Table S14\textsuperscript{97, 121, 162-164}). Data from 10-year follow-up reported higher incidence of renal flares in patients treated with tacrolimus during the induction phase (53\% vs 34\%), while long-term kidney function was similar between the 2 groups.\textsuperscript{164} A more recent open-label clinical trial randomized 314 patients to tacrolimus (target trough level 4-10 ng/ml) or i.v. cyclophosphamide and reported non-inferior 6-month responses between groups, with similar rates of adverse events (Supplementary Table S15\textsuperscript{165-167}).\textsuperscript{167}
Practice Point 10.2.3.1.5: A triple immunosuppressive regimen of belimumab with glucocorticoids and either MPAA or reduced-dose cyclophosphamide may be considered in patients with repeated renal flares or at high-risk for progression to kidney failure.

A phase 3 RCT of belimumab (10 mg/kg i.v. on days 1, 15, and 29, then every 28 days to week 100) added to standard-of-care therapy resulted in approval of belimumab for LN by the U.S. FDA in December 2020. This trial, BLISS-LN, examined the 2-year PERR when belimumab or placebo was added to standard-of-care therapy, which was either MMF or the Euro-Lupus reduced-dose cyclophosphamide regimen chosen by the site investigator. PERR was defined as a ratio of PCR of <0.7, an eGFR that was no worse than 20% below baseline or at least 60 ml/min per 1.73 m², and no use of rescue therapy for treatment failure. At week 104, significantly more patients who received belimumab achieved a PERR compared to patients who received placebo (43% vs. 32%; OR 1.60; \( P = 0.03 \); Supplementary Table S11). Key secondary endpoints included complete renal response and the risk of renal event or death. These also favored belimumab. Subgroup analysis showed that the overall PERR response was driven by the results in the larger subgroup (73.5%) of patients who received MMF as background therapy. Belimumab treatment was not associated with excess adverse events. Although not directly tested in the BLISS-LN trial, subcutaneous belimumab has been shown to achieve similar exposure to intravenous. Subcutaneous belimumab is administered at 200 mg weekly. An important observed effect of belimumab therapy in the BLISS-LN trial was the prevention of disease flares. The follow-up for 2 years and an open-label follow up for additional 6 months reported better preservation of kidney function and reduced incidence of adverse kidney outcomes when belimumab was added to standard-of-care therapy.

In post hoc subgroup analysis of this study, the efficacy benefit of belimumab appeared restricted to patients who received MMF but not those treated with cyclophosphamide, and in patients with proteinuria in the non-nephrotic range. Also, those who self-identified as Black race, although only 63 of 446 total number of patients in the trial, appeared to have a lower response rate to treatment compared with other racial groups but had a higher response rate when treated with belimumab compared with placebo.

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.

Azathioprine combined with methylprednisolone pulses showed a comparable short-term renal response rate to that for prednisolone combined with standard-dose i.v. cyclophosphamide in a study that included 87 patients in the Netherlands, but the azathioprine and pulse methylprednisolone group had more infections, and their extended follow-up data showed a higher relapse rate and greater progression of CKD (Supplementary Table S16). Nonetheless, some patients may not tolerate MPAA, cyclophosphamide, or CNIs, or these drugs may be unavailable, too costly in some regions of the world, or contraindicated, as in pregnant patients.

Short-term studies in Chinese patients compared leflunomide against i.v. cyclophosphamide, in both cases combined with glucocorticoids, and reported comparable renal response rates of approximately 70% after 6 months. It should be noted that leflunomide may cause birth defects and has a long elimination half-life of over 2 weeks, and its active metabolite is highly bound to plasma proteins, so that patients who have taken leflunomide must stop treatment for at least 2 years before trying to conceive.
Other therapies that have not shown significant benefit when added to standard therapy include plasmapheresis (Supplementary Table S1718, 61, 175-178), and the anti-interleukin-6 antibody sirukumab (Supplementary Table S18179). In a phase 2a trial, laquinimod was associated with a higher renal response rate (62.5% compared with 33.3% in the placebo group) when added to standard-of-care treatment with glucocorticoids and MMF in patients with active LN (Supplementary Table S19180).

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.

Results from phase 2 and phase 3 clinical trials did not demonstrate superiority in efficacy when B cell–targeting therapies (rituximab, ocrelizumab), costimulatory blockade (abatacept), or anti-interleukin-6 monoclonal antibody were added to standard initial therapy of glucocorticoids and either MMF or cyclophosphamide. The negative outcomes contrast with reports of case series that suggested efficacy when patients with suboptimal response to standard therapy were treated with rituximab. Interestingly, patients treated with rituximab and abatacept in the RCTs showed more effective suppression of anti-double-stranded deoxyribonucleic acid (dsDNA) levels and complement activation, but this biological efficacy did not translate to conventional clinical indicators of treatment response. Reasons for the apparent discrepancy between biological efficacy versus clinical observations, and between the case series versus RCT results, include the different populations of patients studied, the outcome parameters used in the trials, and the relatively short duration of observation in the trials. Some trials using biologics have yielded encouraging results. For example, in a prospective single-center pilot study to investigate whether rituximab could facilitate corticosteroid avoidance, 50 patients with active LN (22 Class V, 28 Class III/IV ± V) were treated with rituximab 1 g and methylprednisolone 500 mg i.v. on day 1 and day 15 and were maintained on MMF (maximum dose 1.5 g twice per day, target trough blood level of mycophenolic acid 1.2–2.4 μg/ml [3.7–7.5 μmol/l]) without glucocorticoids, and by 52 weeks, 52% of patients achieved complete remission and 34% achieved partial remission.

The negative outcomes in previous clinical trials do not preclude a therapeutic role for some of these novel agents in selected patients, including those who have not responded well to or who do not tolerate standard therapy, or when steroid-sparing is attempted (Supplementary Tables S20–S23). Ongoing clinical trials continue to investigate the role of biologics for the treatment of LN. A recent phase 2 study showed that in adult patients with active proliferative LN treated with MPAA and glucocorticoids, the addition of obinutuzumab resulted in higher complete renal response rates at week 76 (40% vs. 18%, P = 0.007), and at week 104 compared to placebo (54% vs. 29%, P = 0.005). The rate of serious adverse events and serious infections did not differ between the 2 groups.

Anifrolumab is a human monoclonal antibody that binds to the type I interferon receptor unit 1 and has been recently approved by the FDA for treatment of non-renal SLE. In a phase 2 clinical trial that randomized 147 patients to a basic (anifrolumab 300 mg), intensified (anifrolumab 900 mg), or placebo added to MPAA standard of care therapy, anifrolumab was associated with numerically higher renal response rate (45.5 % vs 31.1% in placebo group). As potential benefit of anifrolumab was suggested by exploratory endpoints of response, a phase 3 trial is ongoing (NCT02547922).

In summary, there are accumulating data on the biological and clinical efficacy of various biologic and non-biologic therapies. Although long-term results are awaited, results on these new drugs have expanded the armamentarium of therapeutic options and potential combinations of treatments. The favorable safety profile associated with some of the new drugs presents a distinct advantage. Further
investigations are necessary to define the profiles and characteristics of patients who would benefit most from each of the various novel therapies.

### 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).

This recommendation places a high value on the data demonstrating that long-term, reduced-dose MPAA decrease the risk of LN relapse compared to azathioprine or no treatment and that MPAA have effectiveness comparable to that of cyclophosphamide but with a lower risk of adverse events. The recommendation places a lower value on the risk of adverse events associated with long-term MPAA treatment as compared to no treatment (Figure 8).

**Figure 8 | Recommended maintenance therapy for Class III and Class IV lupus nephritis.** The target ranges for CNIs have been based on the transplant literature. The KDIGO Work Group acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, the most reasonable dosing of a CNI may be to titrate in the individual patient to obtain the desired effect on proteinuria, balancing dose escalation against serum creatinine level, reducing the dose if serum creatinine level increases but does not plateau or increases over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. CNI, calcineurin inhibitor; MPAA, mycophenolic acid analogs.
Key information

Balance of benefits and harms

High-intensity immunosuppression for the initial treatment of LN is given for 3–6 months, depending on the regimen (Section 10.2.3.1). At the end of initial therapy, only about 10%–40% of patients achieve complete response as defined by clinical parameters, and approximately 20% achieve complete histologic remission, defined as an activity index of zero on repeat kidney biopsy. Also, LN relapses frequently, and relapses predispose to additional kidney damage and progression to kidney failure. Ongoing treatment is therefore needed to consolidate initial responses into more complete and sustained responses, and to prevent disease flares. After initial therapy, ongoing immunosuppression is designated as maintenance therapy.

The evolution of current maintenance therapy for proliferative LN is an example of how investigators have tried to balance preservation of kidney function against the toxicities of long-term immunosuppressive therapy. After it became clear that the addition of a cytotoxic agent to glucocorticoids during the initial treatment of LN improved long-term kidney survival, patients were kept on oral, or in later studies i.v., cyclophosphamide for months or years. This led to considerable lifetime cyclophosphamide exposure and toxicity. A study reported in 2004 compared quarterly i.v. cyclophosphamide against oral MMF or azathioprine for LN maintenance, and the results showed not only a significant reduction in side effects in those treated with MMF or azathioprine but also improved kidney and patient outcomes compared to the cyclophosphamide group. This led to a decrease in the use of quarterly cyclophosphamide as maintenance treatment. Favorable long-term results with sequential immunosuppressive regimen have been published by others, and together, they ushered in the current era of intense, high-dose immunosuppression for the initial treatment of proliferative LN, followed by prolonged immunosuppression with a less intense regimen to reduce adverse events while ensuring the continued suppression of immune-mediated pathogenic processes so that the response following initial therapy is consolidated, the disease remains quiescent, flares are prevented, and further damage to the kidney or other organs is avoided.

MMF and azathioprine were directly compared as maintenance agents in 2 major clinical trials (Supplementary Table S2). In an LN cohort of 227 ethnically diverse patients, the maintenance phase of ALMS showed that over 3 years of follow-up, the composite treatment failure endpoint of death, kidney failure, LN flare, sustained doubling of SCr, or requirement for rescue therapy was observed in 16% of MMF-treated patients and in 32% of azathioprine-treated patients \((P = 0.003)\). LN flares occurred in 12.9% of MMF-treated patients and 23.4% of azathioprine-treated patients. In contrast, the Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis (MAINTAIN) trial randomized 105 predominantly White patients to MMF or azathioprine and glucocorticoid maintenance therapy after initial therapy with the low-dose cyclophosphamide regimen and showed no difference in time to kidney flare between the 2 groups, with a cumulative kidney flare rate of around 20% in both groups after 36 months. A higher proportion of patients in the azathioprine group had adverse events leading to withdrawal of therapy in the ALMS maintenance trial (39.6% vs. 25.2%), and there was a higher incidence of cytopenia in the azathioprine group in the MAINTAIN trial. Thus, in most LN populations, MMF (MPAA) is the maintenance drug of choice.

An RCT compared maintenance treatment with triple immunosuppression that included low-dose MPAA, low-dose tacrolimus, and low-dose glucocorticoids (“multitarget” regimen) against azathioprine in responders following “multitarget” regimen or the NIH i.v. cyclophosphamide regimen as initial treatment for 6 months in the 2 groups respectively, and the results showed similar efficacy in preventing flares in the 2 groups and a higher incidence of adverse events due to transaminitis in the azathioprine group. However, the follow-up duration of 18 months was relatively short, and the generalizability of data needs further investigation. Also, although the response rate was significantly
higher in the “multitarget” group after 6 months of initial treatment, the cumulative response rate was similar between the 2 groups during the second year of therapy, increasing to approximately 90% by the end of 24 months.

There are recent reports on relatively favorable results, albeit with relatively short-term follow-up, with various triple immunosuppressive maintenance treatment regimens that comprised glucocorticoids with MPAA or reduced-dose cyclophosphamide, and either a CNI (cyclosporine\textsuperscript{197, 198}, tacrolimus,\textsuperscript{199} voclosporin\textsuperscript{104, 106}) or belimumab (Figure 9).\textsuperscript{107, 109}

Based on these considerations collectively, the Work Group concluded that the benefits of maintenance immunosuppression far outweigh its potential harms, and MPAA is the preferred drug based on the data to date (Practice Point 10.2.3.2.1), while there is the need for more data on how long to extend triple immunosuppressive regimens with belimumab or CNIs, and the way to taper maintenance immunosuppression.

\textbf{Certainty of evidence}

Three RCTs compared azathioprine with mycophenolate mofetil. There was moderate certainty of evidence for renal relapse, kidney function and leucopenia due to serious imprecision in the estimate of effects, and low or very low certainty of evidence for other outcomes due to study limitations and/or very serious imprecision (Supplementary Table S24\textsuperscript{12, 194-196}).

Only 1 RCT compared long duration (18 months) of cyclophosphamide therapy encompassing both the initial treatment period and the maintenance phase with short duration (6 months) of cyclophosphamide therapy as initial treatment followed by maintenance treatment with variable immunosuppressive regimens. Due to study limitations and very serious imprecision (only 1 study, and very wide CIs, indicating appreciable benefit and harm), the certainty of the evidence for this trial is very low (Supplementary Table S25\textsuperscript{114}).

Similarly, only 1 RCT (n = 39) compared azathioprine with quarterly pulse cyclophosphamide as maintenance treatment, indicating very low certainty of the evidence because of study limitations and very serious imprecision (only 1 study, wide CIs) (Supplementary Table S26\textsuperscript{194}).

The ALMS trial compared azathioprine with MMF as maintenance therapy in patients with proliferative LN and showed an increased rate of composite “treatment failure” endpoint and adverse effects (e.g., leukopenia) in patients who received azathioprine.\textsuperscript{16} Despite the large sample size and the fact that this was an RCT, the certainty of the evidence was downgraded to moderate because of imprecision (few events) or study limitations (unclear allocation concealment).

Data on the use of CNIs or mizoribine exclusively added to the maintenance treatment are generally of low certainty (Practice Point 10.2.3.2.4\textsuperscript{200-203}), and there is a lack of information regarding addition of B-cell directed therapies to the maintenance phase.

\textbf{Values and preferences}

In the judgment of the Work Group, most well-informed patients who have undergone aggressive immunosuppression to control their LN would choose maintenance therapy to try to attain complete remission if it had not yet been achieved, and in all cases to avoid disease relapses needing reinstitution of high-dose immunosuppression. In the judgment of the Work Group, the better efficacy of MPAA with its generally favorable tolerability profile, compared to azathioprine, attests that most well-informed patients would choose MPAA as the first-line treatment.

However, patients who have had severe adverse effects while on MPAA, or who place a high value on becoming pregnant, may choose azathioprine (or a CNI) over MPAA, as may patients for whom MPAA is unavailable or unaffordable.
**Resource use and costs**

In general, it is reasonable to assume that the personal and societal cost of not using maintenance therapy and risking disease relapse after investing in initial therapy would be higher than the cost of maintenance medications. Compared with initial therapy, facility costs are often lower, as maintenance regimens are oral, and outside of medication expense, with major resource implications arising from laboratory monitoring of lupus activity and immunosuppression and managing complications of treatment. Although the drug cost of MPAA is considerably higher than that of azathioprine, there are few cost-effectiveness analyses of maintenance treatment for LN. Also, some drugs may have limited accessibility in certain regions, and this may influence choices. Drug-level monitoring is required in patients treated with some CNIs, but not when azathioprine or MPAA is used, and this also has implications for affordability and accessibility.

**Considerations for implementation**

Apart from availability and cost of MPAA, a major consideration for implementation of maintenance therapy is safety during pregnancy. It is not advisable to attempt pregnancy until LN and SLE have been well-controlled for some time, which would give ample opportunity to switch patients over to a regimen that is safe during pregnancy. Pregnancy decisions are complex, and maintenance therapy often needs to be individualized on this basis (Section 10.3.2.). MPAA is contraindicated during pregnancy and must be discontinued well in advance of trying to conceive. Cyclosporine is classified under category C by both the Therapeutic Goods Administration (TGA) in Australia and the FDA in U.S., while tacrolimus is classified under category C by TGA and not assigned a category by FDA. Data from animal studies showed potential adverse effects which appeared dose-related. With regard to human pregnancy, category C means risk cannot be excluded but the experience to date, mainly from organ transplant recipients, is generally favorable with both cyclosporine and tacrolimus, showing an increased incidence of low birth weight but not fetal malformations. Prescribing information from the manufacturer of voclosporin states to avoid its use in pregnant women due to the alcohol content of the drug formulation, while there is insufficient data to conclude whether there is a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Data from animal studies showed embryo/fetal effects, but no treatment-related fetal malformations. In this regard most preparations of cyclosporine also contain alcohol. Low-dose azathioprine is safe during pregnancy.

There is not enough data on the safety of belimumab during pregnancy and its use cannot be recommended at this time.

**Rationale**

The use of maintenance combined immunosuppressive therapy in Class III/IV LN to consolidate response to initial immunosuppressive treatment and prevent disease flares is supported by evidence of at least moderate certainty. There are more robust data supporting the superiority of MPAA over azathioprine as maintenance therapy, from clinical trials that included patients of different races and ethnicities. Information from the clinical trials using belimumab first as initial therapy then continued for 2-2.5 years as maintenance therapy suggest a lower risk for disease relapses based on post hoc analysis with low certainty of evidence.

**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.
As discussed under Recommendation 10.2.3.2.1, the direct comparison between MPAA and azathioprine as maintenance treatment in LN, both combined with low-dose glucocorticoids, is mainly based on data from ALMS and the MAINTAIN trial. Although the results from the latter showed no statistically significant difference in time to disease flare or long-term clinical outcomes in Caucasian patients, data from ALMS based on a large sample size from different countries with different ancestry demonstrated superior efficacy of MPAA compared with azathioprine, and in both trials, azathioprine was associated with more adverse effects, such as leukopenia and abnormal liver-enzyme levels. However, azathioprine is much cheaper than MPAA, and financial barriers may limit access to MPAA in many countries. Under such circumstances, or in patients who do not tolerate MPAA because of side effects, low-dose glucocorticoids combined with azathioprine are an effective maintenance immunosuppressive treatment. Observational cohort data from Chinese patients showed that in patients who received MPAA as initial therapy, the disease flare rate was increased when the total duration of MPAA was <2 years, and that long-term maintenance treatment with MPAA was associated with a low disease flare rate. Overall, although the efficacy and safety data to date favor MPAA as maintenance treatment, azathioprine is an acceptable alternative, especially in the later phase of long-term management.

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.

Prolonged glucocorticoid exposure is associated with continued and significant organ damage accrual and morbidity. At the end of the initial phase of treatment, the goal is to have reduced most patients to a daily dose of prednisone (or equivalent) that is ≤7.5 mg, and preferably as low as possible. The tapering regimen and duration of glucocorticoid maintenance therapy vary considerably among clinicians and are largely opinion-based, informed by individualized considerations of a patient’s risk of developing disease flare, and the risk–benefit balance of the prevailing dose of immunosuppressive medications. A recent open-label controlled trial (Evaluation of the Discontinuation of Maintenance Corticosteroid Treatment in Quiescent Systemic Lupus [CORTICOLUP] trial) compared continuation of prednisone 5 mg daily against discontinuation in 124 multiethnic patients in Paris with stable and quiescent SLE (history of LN in 34% and 41%, respectively). The results showed a significantly increased flare rate over 52 weeks of follow-up in patients who discontinued prednisone (HR: 0.2 in those who continued prednisone 5 mg daily, \( P = 0.002 \)), and 45 of 63 patients in the discontinuation group remained glucocorticoid-free. Glucocorticoid discontinuation in patients with stable quiescent disease can be considered, but it should be undertaken with caution and careful monitoring for disease flare. Glucocorticoid avoidance in maintenance therapy has been attempted with the use of rituximab, but the evidence to support this approach remains limited to one cohort.

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 mycophelolic acid (MPA), approximately 540–720 mg twice daily.

The suggested dosages are largely based on data from the ALMS and MAINTAIN trial. As mentioned before, the Work Group recommends maintenance of these doses until achievement of complete response and then tapering. Due to pharmacogenetic differences, the level of MPA exposure varies considerably among patients receiving the same dose of MPAA. Although there are insufficient data to date to provide recommendations on therapeutic drug monitoring, measurement of MPA exposure may be helpful in patients with unsatisfactory treatment response or who manifest drug
toxicities. There are preliminary data associating disease flares with low MPA exposure, but optimal drug level at different phases of clinical management remains to be determined.209

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

The optimal duration of maintenance immunosuppression in patients with proliferative LN is not known. If withdrawn too early, patients may relapse even after having had a good response to treatment. Prolonged maintenance increases exposure to immunosuppression and may not provide sufficient continued benefits to outweigh toxicity risk. The Work Group recommends that the total duration of immunosuppression (initial therapy plus maintenance) for patients with proliferative LN who have achieved a complete renal response and have no ongoing extrarenal manifestations be ≥36 months, based on considering the following evidence collectively:

- In a recent clinical trial (Weaning of Immunosuppression in Nephritis of Lupus [WIN-Lupus]) from France, 96 patients who responded to initial therapy and with proteinuria below 0.5 mg/g between 2 to 3 years were randomized to immunosuppression discontinuation over 3 months or continuation and were observed for 24 months. The study was underpowered, but after 2 years there were more severe SLE flares and a trend for higher renal relapses in the discontinuation group (Supplementary Table S27).210

- In Chinese patients who received MMF as initial therapy, discontinuation of MMF before 2 years was associated with an increased risk of disease flare.15, 113

- During the third to fourth year of MMF maintenance therapy, kidney flare was associated with low 12-hour trough MPA blood levels, whereas patients with trough levels of approximately 2 mg/l remained in remission.211

- The ALMS maintenance phase data reported a relatively high incidence of treatment failure (16%–32%) and kidney flares (13%–23%) despite 36 months of immunosuppression and maintenance with low-dose glucocorticoids and either MMF or azathioprine.16

- In an Italian cohort, immunosuppression was tapered in patients who were in complete remission for >12 months, and 27% relapsed. One of the predictors of successful treatment discontinuation was a longer duration (median of 4 years) of prior immunosuppressive therapy.212

- Despite ≥36 months of immunosuppression and ≥12 months of sustained complete clinical renal response, 28%–50% of patients continue to show inflammatory histologic activity on repeat kidney biopsy.213-215 Patients with persistent histologic activity have an increased risk of LN flare after maintenance immunosuppression is discontinued, compared to patients who have no residual inflammatory activity in their kidneys.214, 215

- Patients who have achieved a partial remission tend to be left on maintenance immunosuppression indefinitely. Kidney biopsy studies of such patients have shown that many have resolution of histologic activity,213-215 but are clinically only in partial remission due to residual proteinuria. In such patients, proteinuria may reflect CKD as opposed to active disease, and immunosuppression may be able to be discontinued in the absence of ongoing kidney inflammation.
In summary, despite not knowing the optimal duration of maintenance immunosuppression for proliferative LN, most patients will require ≥3 years of therapy. Clinical response findings do not correlate completely with ongoing kidney inflammation. A repeat kidney biopsy could be considered to inform the decision to continue or withdraw maintenance immunosuppression.

**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 triple immunosuppressive regimen as maintenance therapy (Figure 9).

In the phase 3 belimumab trial in LN (BLISS-LN) patients in the intervention arm were treated with low-dose glucocorticoids and belimumab plus either MPAA or azathioprine as maintenance immunosuppression, and treatment was continued till 100 weeks from baseline with the primary endpoint assessed at week 104. This was followed by an open-label extension study of 28 weeks that included 257 of the original 448 patients randomized in BLISS-LN trial, during which patients originally randomized to receive placebo were changed to belimumab. Results from the latter showed that the efficacy benefit associated with belimumab treatment was maintained with no safety concerns; and post-hoc analysis showed that patients treated with the belimumab-containing triple immunosuppressive regimen had lower rates of adverse kidney outcomes as well as better kidney function.

In the phase 3 voclosporin trial in LN (AURORA 1) treatment was continued for 52 weeks and the primary endpoint assessed at week 52. Patients who completed the phase 3 trial were eligible to continue the same blinded therapy in a 2-year continuation study (AURORA 2; 116 of 179 patients in the voclosporin arm and 100 of 178 patients in the control arm). Results from the latter showed sustained reduction of proteinuria with voclosporin treatment, and stable and similar kidney function in both groups, with no safety signal.

In a trial of 368 Chinese patients that compared triple immunosuppression with glucocorticoids and fixed-dose tacrolimus and reduced-dose MMF against glucocorticoids and sequential cyclophosphamide followed by azathioprine, patients continued with the triple immunosuppressive regimen for 24 months. By the end of 24 months, the 2 treatment arms showed similar complete remission rates approaching 80% and patients treated with triple immunosuppression showed a relapse rate of 5.47%, with a lower withdrawal rate due to adverse events (1.7%) compared with controls (8.9%).

These results suggest that triple immunosuppressive regimens that include belimumab or a CNI in addition to standard maintenance immunosuppression can be continued for 2–3 years.

**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).

Experience in Japanese patients suggested that low-dose tacrolimus at 3 mg/d was safe and effective when given as long-term maintenance therapy together with low-dose glucocorticoids. In a study of 70 Chinese patients who achieved remission after initial therapy with glucocorticoids and either i.v. cyclophosphamide or tacrolimus, maintenance therapy with tacrolimus (trough blood level target of 4–6 ng/ml [5–7.4 nmol/l]) was compared with azathioprine 2 mg/kg/d, both in combination with prednisone 10 mg/d. Over 6 months of follow-up, kidney relapse occurred in 2 azathioprine-treated patients and in none in the tacrolimus group.

Adding tacrolimus or cyclosporine to maintenance therapy was reported in case series as effective in reducing proteinuria in patients with unsatisfactory suppression of proteinuria following initial therapy.
with glucocorticoids and MMF, especially in patients who showed features of Class V LN in their baseline kidney biopsies. Caution is required when considering adding CNI for the purpose of decreasing proteinuria. It is desirable that there be histologic evidence of podocyte injury so that the CNI is likely to be effective. Also, it is prudent to avoid overimmunosuppression and chronic CNI nephrotoxicity, especially in patients with CKD.

Although most studies were done in patients of Asian origin, it is reasonable to consider a CNI for maintenance therapy in any patients who cannot take MPAA or azathioprine. Tacrolimus and cyclosporin can also be used safely during pregnancy (Figure 9).

The experience with mizoribine as maintenance therapy in LN is largely limited to Japanese patients. Results from a post-marketing surveillance study that included 559 mizoribine-treated patients showed that nearly all were receiving glucocorticoids, and 43.8% were receiving tacrolimus as concomitant treatment. Overall, 63.3% of patients achieved complete or partial remission, and only 3.6% of patients experienced serious adverse drug reactions within 2 years of mizoribine treatment, and the authors concluded that mizoribine was safe and effective (Figure 9).

Leflunomide is a prodrug that once metabolized inhibits de novo pyrimidine nucleotide biosynthesis. An open label 36-month trial from China randomized 270 LN patients with previous response to i.v. cyclophosphamide therapy to leflunomide 20 mg/d or azathioprine (target dose 100 mg/d) and oral glucocorticoids. No difference in renal flares was observed between groups by 36 months (15.7% vs 17.8%), and the kidney function was similarly preserved in both groups. No differences in adverse events were observed between groups (Supplementary Table S28). There are no formal studies comparing leflunomide and MPAA, therefore leflunomide is exclusively considered an alternative to MPAA in the above mentioned circumstances. Leflunomide is contraindicated in pregnancy and should be discontinued for at least 2 years before trying to conceive.

<table>
<thead>
<tr>
<th>Maintenance immunosuppressive regimens</th>
<th>Low-dose glucocorticoids AND</th>
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<tbody>
<tr>
<td>Mycophenolic acid analogs</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Belimumab and mycophenolic acid analogs or azathioprine</td>
<td>CNI and mycophenolic acid analogs</td>
</tr>
<tr>
<td>Comments</td>
<td>Preferred treatment based on high-certainty evidence; lower flare rate than azathioprine maintenance</td>
</tr>
<tr>
<td></td>
<td>Low medication cost; safe in pregnancy</td>
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<tr>
<td></td>
<td>Efficacy and safety of belimumab demonstrated in BLISS-LN (104-wk) and open-label extension trials (28-wk) [Practice Point 10.2.3.2.5]</td>
</tr>
<tr>
<td></td>
<td>Efficacy and safety of voclosporin demonstrated in AURORA 1 (52-wk) and AURORA 2 continuation trials (2-yr); efficacy and safety of tacrolimus demonstrated in ‘Multitarget Therapy’ trial in Chinese patients in which tacrolimus and reduced-dose MPAA were given for 24 months [Practice Point 10.2.3.2.5]</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus and cyclosporine safe in pregnancy; insufficient pregnancy data on voclosporin</td>
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<tr>
<td></td>
<td>Experience mostly in Japanese patients</td>
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</table>

Figure 9 | Maintenance immunosuppressive regimens in patients with lupus nephritis. AURORA, Aurinia Renal Response in Active Lupus with Voclosporin; AZA, azathioprine; BLISS-LN, Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis; CNI, calcineurin inhibitor; LN, lupus nephritis; MPAA, mycophenolate acid analogs.

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 10.
Class V LN accounts for 5%–10% of all LN cases. Data on clinical management are based on very few RCTs with small sample sizes, analyses of pooled data, and observational studies. Because 10%–30% of patients with Class V LN and nephrotic proteinuria progress to kidney failure during long-term follow-up, heavy proteinuria does not usually spontaneously remit, as it may in primary membranous nephropathy, and as heavy proteinuria increases CV morbidity and predisposes patients to thrombosis, treatment of Class V patients who have nephrotic-range proteinuria or nephrotic syndrome is warranted.224-227

A small RCT demonstrated that remission was significantly more likely with prednisone plus cyclophosphamide (60%) or prednisone plus cyclosporine (84%) than prednisone alone (27%), but cyclophosphamide maintained remission longer (no relapses within a year) than CNI treatment (40% relapsed within a year of discontinuing the CNI).143 Pooled data from 2 studies showed that prednisone plus either cyclophosphamide or MMF had similar efficacy in lowering proteinuria after 6 months of treatment.228 Other studies with relatively small sample sizes reported the efficacy of glucocorticoids combined with azathioprine,27, 211 oral cyclophosphamide,229 i.v. cyclophosphamide,143, 230 MMF,26, 27, 162, 230-232 CNIs,143, 162, 219, 233-235 and rituximab,190, 236 with response rates of 40%–60%. Tacrolimus was reported as effective when given together with glucocorticoids as initial therapy to patients with Class V LN who presented with NS, or when given as add-on therapy to patients with mixed Class V and Class III/IV LN whose proteinuria response was judged suboptimal after initial treatment with prednisolone and MMF.201 In the phase 3 voclosporin trial (AURORA; see Practice Point 10.2.3.1.5), 14% of the patients had pure Class V LN.159 Although adding voclosporin to background therapy was more effective than background immunosuppression alone in achieving renal response, the details on the patients with Class V have not been presented. There is a lack of robust data in the management of Class V LN, especially in patients who present with nephrotic syndrome. The data to date are more in favor of combining glucocorticoids with MPAA, a CNI, or short-term cyclophosphamide than with other options.

In addition to general methods to reduce urine protein, such as renin-angiotensin system inhibitors and meticulous blood pressure control, MMF is a reasonable first choice for treating patients with Class
V and nephrotic-range proteinuria. If ineffective, we suggest cyclophosphamide for \( \leq 6 \) months next in an effort to induce long-term remission, but long-term CNI or rituximab may also be tried if the patient has had prior significant exposure to cyclophosphamide or is reluctant to take the medication in view of the associated toxicities. Appropriate measures to prevent venous thrombosis should be considered in patients whose proteinuria persists despite treatments (see Chapter 1 of the KDIGO Guideline on Glomerular Diseases).

**10.2.4.1 Assessing treatment response in LN**

**Practice Point 10.2.4.1.1:** Definitions of response to therapy in LN are provided in Figure 11.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tr>
<td><strong>Complete response</strong></td>
<td>Reduction in proteinuria (&lt;0.5\ g/g \ (50\ mg/mmol)) measured as the PCR from a 24-h urine collection</td>
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<tr>
<td></td>
<td>Stabilization or improvement in kidney function ((\pm 10%)–15% of baseline)</td>
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<td></td>
<td>Within 6–12 mo of starting therapy, but could take more than 12 mo</td>
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<tr>
<td><strong>Partial response</strong></td>
<td>Reduction in proteinuria by at least 50% and to (&lt;3\ g/g \ (300\ mg/mmol)) measured as the PCR from a 24-h urine collection</td>
</tr>
<tr>
<td></td>
<td>Stabilization or improvement in kidney function ((\pm 10%)–15% of baseline)</td>
</tr>
<tr>
<td></td>
<td>Within 6–12 mo of starting therapy</td>
</tr>
<tr>
<td><strong>No kidney response</strong></td>
<td>Failure to achieve a partial or complete response within 6–12 mo of starting therapy</td>
</tr>
</tbody>
</table>

Figure 11 | Commonly used definitions of response to therapy in lupus nephritis. *For children <18 years old, complete response is defined as proteinuria <0.5 g/1.73 m\(^2\)/d or <300 mg/m\(^2\)/d based on a 24-h urine specimen. PCR, protein–creatinine ratio.

All response criteria currently used in clinical trials of LN require improvement in proteinuria and stabilization or improvement in kidney function. Several observational studies suggest that long-term kidney health is considerably more favorable in patients who respond to treatment.\(^{110, 237-239}\) However, there are no universally accepted criteria for the level of improvement required, which makes direct comparisons of different clinical trials more difficult.

The definitions in Figure 11 are commonly used with “baseline” kidney function referring to the level before disease flare, which is not known in patients with no previous medical record. Long-term data from 2 large European LN trials showed that favorable kidney outcomes were predicted by achieving a proteinuria level of 0.7–0.8 g/d after 12 months of therapy, a conclusion supported by other reports.\(^{112, 240-242}\) In this regard, renal response at week 104 or week 52 have been used as study endpoints in recent clinical trials such as the phase 3 BLISS-LN study.\(^{107}\)

Another caveat is the lack of consensus on the appropriate time when response should be assessed. For logistic and economic reasons, large clinical trials often evaluate response at 6–12 months, but improvement of proteinuria and eGFR is continuous over time, and the rate of improvement varies considerably among patients. Also, there are marked differences in baseline kidney abnormalities at disease presentation. Therefore, the time to reach prespecified proteinuria and eGFR cutoffs, either absolute or relative to baseline, varies considerably among patients.\(^{12, 14, 15, 144, 219, 243, 244}\)

Outside of a formal clinical trial setting, the Work Group suggests that if patients are improving, allowing 18–24 months to achieve a complete response is reasonable in patients who show continuous improvement. A potential tool to predict kidney outcomes was derived from a post hoc analysis of the large ALMS trial. This analysis suggested favorable kidney outcomes are predicted by normalization of complement levels and \(\geq 25\%\) reduction of proteinuria after 8 weeks of treatment.\(^{245}\)
SLE is a systemic disease, and the kidney should not be examined in isolation from other clinical manifestations. Several other clinical parameters have not been evaluated in detail in clinical studies but are relevant at individual levels such as systemic activity of SLE (e.g., SLEDAI score), blood pressure control, edema resolution, urine sediment, hemoglobin and albumin improvements, and serologic parameters, including dsDNA antibodies and serum complements. If lupus serologies are abnormal, it is reasonable to expect improvement with therapy for LN, although many patients remain positive for anti-dsDNA and/or have low complement levels despite resolution of proteinuria. Extrarenal lupus activity requiring continuation or a change in therapy could remain even if the kidney improves. Finally, response is currently only assessed clinically. Considerable data suggest that persistent intrarenal lupus activity may remain, despite resolution of proteinuria and eGFR. A repeat kidney biopsy may, therefore, be useful in confirming renal response, especially before important major treatment decisions such as discontinuation of immunosuppression.

10.2.4.2 Management of unsatisfactory response to treatment

Practice Point 10.2.4.2.1: An algorithmic approach to patients whose response to therapy is deemed unsatisfactory is provided in Figure 12.

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<table>
<thead>
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<tbody>
<tr>
<td>1</td>
<td>Verify adherence to treatment</td>
</tr>
<tr>
<td>2</td>
<td>Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)</td>
</tr>
<tr>
<td>3</td>
<td>Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)</td>
</tr>
<tr>
<td>4</td>
<td>Consider switching to an alternative first-line regimen when there is persistent disease activity</td>
</tr>
<tr>
<td>5</td>
<td>Consider the following in patients refractory to first-line treatment regimens: • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide • Enrollment in clinical trials if eligible</td>
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**Figure 12** | Management of patients who show unsatisfactory response to initial therapy for active lupus nephritis. i.v., intravenous.

Judging the response to therapy as unsatisfactory is difficult because there are no robust data with which to compare an individual’s response trajectory, and there needs to be a balance between giving a patient sufficient time to respond and the likelihood of ongoing nephron loss. Nonetheless, patients are expected to show improvement over time after treatment. So, no improvement or worsening despite treatment for 3–4 weeks is clearly unsatisfactory and warrants early appraisal of potential causes for nonresponse and early intervention, whereas patients who show response to treatment can be closely observed and investigated when the level of improvement after 3–4 months of therapy is suboptimal or below expectation. A 2-month time frame to see improvement was suggested based on post hoc analysis of data from the ALMS trial, but deterioration needs to be evaluated on an individual basis in terms of rapidity and severity.

The role of nonadherence in unsatisfactory treatment response cannot be over-emphasized. The prevalence of nonadherence in patients with SLE could be >60%. Switching from oral immunosuppression to i.v. cyclophosphamide should be considered when nonadherence is suspected or proven.
The certainty of evidence on the management of LN “refractory” to standard initial therapy is marred by variable definitions of treatment response or refractoriness, the disparity between kidney histology and clinical outcome parameters, the legacy effect of prior therapy, and the impact of factors other than disease activity on outcome parameters such as proteinuria and kidney function. Available data on the management of refractory disease are largely from uncontrolled observational cohort studies, with varied inclusion criteria and based on relatively small sample size.

The role of switching between therapeutic regimens has not been formally investigated. In a US study that compared mycophenolate with i.v. cyclophosphamide, patients who did not show response, defined as improvement by ≥30%, after 12 weeks of treatment were switched to the other treatment arm. Another study reported efficacy of MMF in patients refractory to or who had relapsed after cyclophosphamide treatment. However, a legacy effect of prior therapy could not be excluded. Unequivocal evidence on the efficacy of switching therapies is lacking.

Evidence supporting the use of rituximab for refractory LN is from open-label observational studies that have reported response rates of 50%–80% and a meta-analysis of 31 studies with 1112 patients that showed complete and partial response rates of 46% and 32%, respectively, after rituximab was added. The role of other biologics with demonstrated efficacy in recent clinical trials, such as obinutuzumab or belimumab, warrants further investigation.

Similarly, data from observational cohorts suggested efficacy of CNIs, combined with either glucocorticoids and/or MMF, in patients with refractory or relapsing LN. Other therapies under investigation may offer potential options for refractory LN, such as anti-CD19 Chimeric antigen receptor T (CAR-T) cell therapy.

10.2.4.3 Treatment of LN relapse

Relapses of LN are common, and LN flare is an important predictor of poor long-term kidney survival. LN flare rates of 10%–50% have been reported, and relapses occur over time. Failure to achieve complete remission increases the risk of subsequent relapse. Relapse rates of 39% and 64% were found in patients who achieved complete remission or partial remission, respectively, and time-to-relapse after complete response was 36 months, compared to 18 months after partial response. Similarly, an HR of 6.2 for relapse was reported in Chinese patients who did not achieve complete remission after initial therapy.

**Practice Point 10.2.4.3.1: 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 first-line therapy.**

There are no data that focus on the treatment of LN flares alone. However, it is generally agreed that there is no major difference between management of an LN flare and that of de novo active LN, and initial therapies are the same as outlined above. Although not yet ready for clinical management, emerging data from a recent transcriptomic study of paired serial kidney biopsies showed slight differences in intrarenal inflammatory gene expression between the initial presentation and LN relapse. All LN clinical trials testing initial, induction therapies for LN include both types of patients. Although these considerations form the basis for Practice Point 10.2.4.3.1, there are several caveats in choosing an approach:

1. If patients had been treated with cyclophosphamide in the past, it is important to calculate lifetime exposure. Ovarian failure has been associated with age (and oocyte reserve) and cumulative dose, with sustained amenorrhea occurring in up to 50% of patients aged >32 years with a cumulative exposure of 8 g/m². The chance of future malignancy increases after a
total exposure of 36 g, so if a patient is approaching this level, cyclophosphamide is better avoided.

2. If patients relapse during pregnancy, treatment choices are more limited. These are discussed in Section 10.3.2.

3. Patient preference and/or tolerance of the initial regimen should be considered. Also, patient adherence should be considered in the choice of treatment.

4. Disease activity should be verified, as proteinuria may be secondary to CKD.

The last point is critical but complex. The same clinical criteria used to diagnose de novo LN are used to diagnose LN flares absent a kidney biopsy. That is, flares are generally considered when proteinuria increases beyond a certain threshold, with or without an active urinary sediment or deterioration of kidney function. Without histology, it is sometimes difficult to determine whether changes in proteinuria are due to active inflammatory kidney injury or reflect progression of chronic damage incurred during preceding episodes of active LN, because there is often discordance between clinical findings and histologic findings.10, 11 The tempo and magnitude of change in proteinuria may help with rapid increases, and large changes often reflect active disease. SLE serologies (e.g., complement, anti-dsDNA) may support a flare diagnosis but need to be evaluated in the context of prior serologic trends. A change from normal to abnormal is more useful than serologic studies that are always normal or always abnormal. Given the risks of immunosuppression, if the diagnosis of flare remains uncertain, a repeat kidney biopsy to assess disease activity versus chronic damage is important to inform treatment decisions.279

In lieu of waiting until LN flares before treating it, some investigators have examined preemptive treatment to prevent flare. A trial in the Netherlands compared “early treatment” of 16 patients to conventional management of 23 patients who increased their anti-dsDNA levels by 25%.280 Prednisone was increased by 30 mg/d in the early treatment group and was tapered back to baseline over 18 weeks. After a mean follow-up of <2 years, 2 major relapses (12.5%, both with LN relapse) occurred in the early treatment group, compared to 20 relapses (87%), 7 of which were major (1 kidney relapse), in the conventionally managed patients. A prospective trial in the U.S. randomized 41 patients who showed an increase in both anti-dsDNA and C3a to prednisone (30 mg/d tapered >4 weeks) or placebo. During a short follow-up (90 days), no patients given prednisone had a severe flare, but 6 placebo patients did, and 3 of the flares were kidney-related.281 A recently published retrospective study of Chinese patients with LN suggested that a moderate increase in immunosuppressive treatment dose was effective in preventing kidney and nonrenal flares without excessive treatment-related adverse effects.209 Taken together, all of these data suggest that impending LN flares may be preventable, at least for some patients, but larger RCTs of sufficient duration are needed before this approach can be endorsed.

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 131.
Figure 13 | Management of patients with lupus nephritis and thrombotic microangiopathy


TMA is a pathologic description of vascular endothelial injury secondary to various etiologies.282 The causes of TMA most relevant to patients with LN are thrombotic thrombocytopenic purpura (TTP), antiphospholipid syndrome (APS), and complement-mediated TMA. However, patients with lupus can also develop TMA due to Shiga-toxin-hemolytic uremic syndrome, infections, drugs, or malignancies.283, 284 The key to a good outcome for TMA in LN is rapid diagnosis and prompt treatment. When appropriate expertise is available, it is preferable that patients with LN and TMA be comanaged with an experienced hematologist. However, some of the serologic and genetic testing needed for a specific diagnosis, such as ADAMTS13 activity or the presence of anti-ADAMTS13 antibodies in the case of TTP, antiphospholipid antibodies, and complement studies may not be available, and even when they are available, they often take considerable time to complete (Figure 13). If TTP is suspected, one may consider using the PLASMIC score,1 and if the score defines an intermediate-to-high risk of TTP, adults should be started on plasma exchange and glucocorticoids while waiting for the investigation results. In children, TTP is less common, and plasma exchange has
been associated with considerable morbidity, so it is acceptable to defer plasma exchange for 24–48 hours until the ADAMTS13 result is available to confirm that the procedure is indicated. 

**TMA due to lupus-associated TTP**

The diagnosis of TTP is mainly reserved for patients with TMA and low ADAMST13 activity (≤10%). The treatment of confirmed TTP in LN is extrapolated from that of acquired TTP and includes plasma exchange, high-dose glucocorticoids, rituximab, and/or caplacizumab (von Willebrand factor inhibitor; Figure 13).

**TMA due to APS**

Antiphospholipid antibodies (aPLA) are found in about 30% of patients with SLE and may be associated with venous and/or arterial macro- or microvascular thrombosis, thrombocytopenia, adverse pregnancy outcomes, and neurologic abnormalities. Kidney damage is a well-recognized complication of APS, presenting as renal artery thrombosis or stenosis, renal vein thrombosis, or injury to the kidney microvasculature, also known as antiphospholipid syndrome (APS) nephropathy. There are few data on the management of APS nephropathy. In a retrospective study of 97 patients with kidney TMA, 62.9% tested positive for aPLA, 38.1% for lupus anticoagulant, and 13.4% had APS. Complete and partial response rates were 38.1% and 22.6%, respectively, after 12 months of immunosuppressive treatment. Thirty-seven of 61 patients who were aPLA-positive also received anticoagulation therapy, and anticoagulated patients showed a higher complete response rate (59.5% vs. 30.8%), and the partial response rate was 18.9% and 26.9% in patients who had or had not received anticoagulant therapy, respectively. Therefore, it is reasonable to treat APS nephropathy with long-term anticoagulation with warfarin. Direct oral anticoagulants are not recommended, as they were inferior to warfarin in preventing thromboembolic events in this setting.

Catastrophic APS is characterized by thrombosis, often of rapid onset, affecting multiple organs, and it is associated with high mortality. Treatment includes both total anticoagulation and high-dose glucocorticoids. Plasma exchange is often used in catastrophic APS and has been associated with improved patient survival in retrospective studies. There are recent anecdotal reports on the potential efficacy of rituximab in catastrophic APS. It has been shown that complement activation is involved in the pathogenesis of tissue injury induced by aPLA, and there is emerging evidence on the efficacy of eculizumab in the treatment of catastrophic APS.

**Complement-mediated TMA and atypical hemolytic uremic syndrome (aHUS)**

Many cases of kidney TMA with ADAMTS13 activity >10% and negative aPLA correspond to complement-mediated TMA, and these patients ideally should be evaluated with complement studies when they are available. aHUS is a rare and severe form of TMA caused by dysregulation of the alternative complement pathway due to genetic or acquired functional defects in complement regulatory proteins, resulting in excessive production of the terminal complement complex C5b-C9, triggering endothelial cell injury that predominantly affects the kidney vasculature in the arterioles and interlobular arteries.

Complement-mediated TMA in LN does not respond well to plasma exchange or immunosuppression with glucocorticoids and cyclophosphamide, and it may be best treated with a complement inhibitor such as eculizumab, although the optimal dose and duration remain controversial. The limited data to date show a high response rate, with resolution of TMA in 68% of patients with secondary aHUS. Data from 31 adult patients (26 treated with plasma therapy and 5 plasma-resistant patients treated with eculizumab) showed complete kidney recovery in 4 of 5 eculizumab-treated patients. Efficacy of eculizumab treatment was also reported in a patients with
lupus and heterozygous deletion in complement factor H CFHR1-CFHR3 gene presenting with TMA, and a review of 20 patients showed a kidney recovery rate of 85% in patients with SLE and/or APS after treatment with eculizumab.317 A recent report on 9 patients with TMA associated with SLE and/or APS showed that kidney function improved by 25% in half of the patients after 4 weeks of eculizumab treatment, and 2 of 3 patients were able to discontinue dialysis.318

Another recent report on 11 patients with TMA and LN showed complement regulatory protein mutations in 6 patients, and response to eculizumab treatment in 10 patients.308

Prior to the advent of eculizumab, plasma exchange and/or plasma infusion was the only treatment for aHUS, with efficacy in less than half of patients and little benefit in patients with membrane cofactor protein mutations.291, 319, 320 As complement studies often take some time to return, initiation of plasma exchange is warranted during the waiting period, or if access to eculizumab is limited. The rationale and objectives of plasma infusion and plasma exchange include the replacement of absent or mutated complement regulating proteins such as complement regulatory genes factor H (CFH) and the removal of antibodies directed to complement regulatory proteins or mutated factors that play a permissive role in aberrant complement activation. In the absence of eculizumab, the efficacy of plasma exchange and plasma infusion varies, and the duration of therapy is dependent on the treatment response.321-324 Data from 31 adult patients (26 treated with plasma therapy and 5 plasma-resistant patients treated with eculizumab) showed recovery of kidney function in approximately 40% of patients given plasma therapy.316

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: Only glucocorticoids, hydroxychloroquine, azathioprine, tacrolimus, and cyclosporin are considered safe immunosuppressive treatments during pregnancy.

Adverse pregnancy outcomes, such as preeclampsia, preterm birth, and fetal loss, are higher in patients with active LN.325, 326 Commonly used medications for LN induction and maintenance therapy, particularly cyclophosphamide and MMF formulations, are toxic to the fetus or teratogenic, respectively. A discussion of acceptable methods of contraception should, therefore, take place as part of initiating treatment for LN. Because of the increased risk of clotting in patients with SLE and antiphospholipid antibodies, use of estrogen-containing birth control should be avoided or minimized. A risk-factor checklist has been proposed by some organizations to stratify, plan, and counsel pregnancy in patients with lupus.327

Hydroxychloroquine is considered safe in pregnancy and may decrease the rate of preterm birth and intrauterine growth retardation, whereas withdrawal of hydroxychloroquine has been associated with LN flare, so it should be continued when an LN patient becomes pregnant.43, 48, 328 Low-dose aspirin (≤100 mg/d) may also reduce the risk of preeclampsia and intrauterine growth retardation and can be started at conception or as soon as pregnancy is recognized.329, 330 The incidence of LN flare in pregnancy has been reported to be 11%–28% and is higher if patients have low serum complement levels or high anti-dsDNA antibody titers.325 Active LN during pregnancy can be treated with glucocorticoids plus azathioprine and/or a CNI, although in the first trimester, the use of glucocorticoids is associated with an increased risk of gestational diabetes and cleft palate. For patients on maintenance
therapy, if they are on azathioprine, this can be continued, but if they are on MPAA, this must be discontinued or changed to azathioprine. Although there is emerging data on the use of belimumab in pregnancy,\textsuperscript{205} this drug is labeled as category C and cannot be recommended for use in pregnancy at this time. Prescribing information from the manufacturer states to avoid the use of voclosporin in pregnant women due to the alcohol content of the drug formulation, while there is insufficient data to conclude whether there is a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Data from animal studies showed embryo/feticidal effects, but no treatment-related fetal malformations.

\subsection*{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.

Approximately 20\% of SLE is diagnosed before the age of 18 years, and genetic components are more common in childhood-onset SLE.\textsuperscript{331-333} There is suggestive evidence that disease is often more severe in the pediatric population. In adolescent patients with SLE and isolated proteinuria, orthostatic or postural proteinuria should be excluded, as this phenomenon has been observed frequently in this population.\textsuperscript{334, 335}

There are few large-scale RCTs to guide treatment of children with LN, and much of the current literature reports the results of adult regimens applied to this population. The data are insufficient to confirm superiority of efficacy for any particular treatment regimen. Several issues must be addressed when treating pediatric lupus, including adherence concerns, which may favor i.v. medications; growth concerns, which may favor limiting glucocorticoid exposure; fertility concerns, especially as patients approach adolescence, which may favor limiting cyclophosphamide exposure; and psychosocial concerns relating to school and socialization with peers. Special considerations regarding glucocorticoid dosing in children are included under Practice Point 10.2.3.1.1. Children with LN should be comanaged by pediatric nephrologists and rheumatologists with expertise in lupus, and the expertise of other professionals, such as clinical psychologists, psychiatrists, or social workers, can be helpful.

\subsection*{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.

There are no data to favor one form of dialysis over another in kidney failure due to LN. Patients with lupus receiving hemodialysis display similar 3-year survival rates and mortality due to CV or infectious complications to those of patients receiving peritoneal dialysis.\textsuperscript{336-338} Therefore, kidney replacement therapy should be individualized, taking into account patient characteristics and preferences.

Kidney transplantation is preferred to dialysis. Kidney transplant outcomes are similar to those in patients who developed kidney failure due to other types of kidney disease,\textsuperscript{339, 340} and transplanted patients have lower mortality than patients with lupus who remain on dialysis.\textsuperscript{341} As clinical outcomes are better in patients with shorter durations of dialysis,\textsuperscript{342, 343} transplantation may be carried out as soon as disease is quiescent. Although lupus activity tends to decrease after kidney failure develops, patients can still flare,\textsuperscript{344} so periodic monitoring is required. LN can recur in kidney allografts, but the risk is low, and flares do not generally result in allograft loss.\textsuperscript{345-347} One important consideration is that patients who have antiphospholipid antibodies may experience dialysis vascular access clotting or allograft thrombosis and may require prophylactic anticoagulation.\textsuperscript{348-350}
Research recommendations

- Identify and validate biomarkers of kidney histology that can be used to follow the tissue response to treatment in real-time to help in managing immunosuppression.
- Identify and validate biomarkers of impending LN flare that can be used to decide if preemptive immunosuppressive therapy is indicated.
- Classify LN on the basis of molecular pathogenesis and histology as opposed to histology alone. This classification ideally could be used in conjunction with novel, targeted therapies for LN to select the most appropriate treatment, including biologic medications targeting specific pathogenic pathways.
- Establish renal response criteria that reflect resolution of disease activity at the tissue level and are also predictive of long-term kidney survival and patient survival without need of kidney replacement therapy.
- Establish criteria for duration of maintenance immunosuppression and the safe withdrawal of therapy.
- RCTs are needed to test the following questions:
  - What is the optimal therapy for patients with severe Class III/IV LN (i.e., patients presenting with severe acute kidney disease and/or markedly abnormal SCr level or eGFR) who have been excluded from the majority of clinical trials to date?
  - What is the optimal therapy for pure Class V LN?
  - Do antimalarials improve the responsiveness of LN to treatment and/or help maintain disease quiescence and prevent flares?
  - Is there a role for complement inhibition in the management of LN?
  - What are the optimal or prioritized therapies for childhood LN?
  - What are the efficacy and safety profiles of CNIs, including the optimal drug exposure when used as initial or maintenance treatment of LN? What are the long-term implications of such treatment?
  - What are the optimal glucocorticoid-reduction protocols for LN management?
  - What is the effect on the incidence of disease relapses of the B-cell directed therapies when initiated during the maintenance phase?
METHODS FOR GUIDELINE DEVELOPMENT

Aim

This is an update of the Lupus Nephritis chapter (Chapter 10) of the KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases published in 2021. Based on the recently published data in the field, it was decided that a guideline update was required.

The objective of this project was to update the evidence-based clinical practice guideline for the management of lupus nephritis. The guideline development methods are described below.

Overview of the process

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3). This guideline has been developed and reported in accordance with the AGREE II reporting checklist.

The processes undertaken for the development of the KDIGO 2023 Clinical Practice Guideline for the Management of Lupus Nephritis included:

- Appointing Work Group members and the ERT
- Defining scope of the guideline update
- Implementing literature search strategies to update the evidence base for the guideline
- Selecting studies according to predefined inclusion criteria
- Conducting data extraction and critical appraisal of the updated literature
- Updating the evidence synthesis and meta-analysis to include newly identified studies
- Updating the quality of the evidence for each outcome
- Finalizing guideline recommendations and supporting rationale
- Grading the strength of the recommendations, based on the quality of the evidence and other considerations
- Convening a public review of the guideline draft in March 2023
- Amending the guideline based on the external review feedback and updating the literature search
- Finalizing and publishing the guideline
Commissioning of Work Group and ERT. The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group, to include content experts in adult nephrology, epidemiology, and public health. The Work Group was responsible for writing the recommendations and practice points and underlying rationale, as well as grading the strength of each recommendation.

For the 2023 update, the Brown University School of Public Health Center for Evidence Synthesis in Health was contracted to update the systematic evidence review and provide expertise in guideline development methodology. The Brown ERT consisted of a senior physician-methodologist who led the ERT for the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis, an adult nephrologist, and librarian-methodologist, all with expertise in evidence synthesis and guideline development, including for KDIGO guidelines. Cochrane Kidney and Transplant was contracted to conduct systematic evidence review and provide expertise in guideline development methodology for the 2021 Guideline.

Defining scope and topics and formulating key clinical questions. Due to resourcing and the probability of practice-changing studies, clinical questions on effectiveness and safety of interventions included in the guideline update were limited to RCTs. Guideline topics and clinical questions focusing on nonrandomized studies were not included in the guideline update (Supplementary Table S1). The guideline Work Group, with assistance from the ERT, determined the overall scope of the guideline. A preliminary list of topics and key clinical questions was informed by the previous KDIGO guideline. The majority of clinical questions for this guideline were based upon RCTs to avoid bias by design. Clinical questions adhered to the PICOM format (a list of critical and important outcomes was compiled after voting from the Work Group [Table 1]). Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accordingly. For clinical questions that did not map to any Cochrane Kidney and Transplant systematic reviews, de novo systematic reviews were undertaken. The previous guideline was reviewed to ensure all identified studies were included in the evidence review. Details of the PICOM questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 2.

All evidence reviews were conducted in accordance with the Cochrane Handbook, and guideline development adhered to the standards of GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).

<table>
<thead>
<tr>
<th>Hierarchy</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical outcomes</td>
<td>All-cause mortality, Kidney failure, ≥50% loss of GFR, Infection, Glucocorticoid-related adverse events, Malignancy</td>
</tr>
<tr>
<td>Important outcomes</td>
<td>Complete remission/relapse, Annual GFR loss (minimum 3 years follow-up)</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate. The critical and important outcomes were voted on by the Work Group using an adapted Delphi process (1–9 Likert scale). Critical outcomes were rated 7–9, and important outcomes were rated 4–6 on the 9-point scale.
<table>
<thead>
<tr>
<th>Guideline chapter</th>
<th>Lupus nephritis (LN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical question</td>
<td>In patients with biopsy-proven LN, compared to no treatment, placebo, or standard of care, does antimalarial therapy improve clinical efficacy outcomes and reduce adverse effects?</td>
</tr>
<tr>
<td>Population</td>
<td>Patients with biopsy-proven LN</td>
</tr>
<tr>
<td>Intervention</td>
<td>Antimalarial therapy</td>
</tr>
<tr>
<td>Comparator</td>
<td>No treatment, placebo, or standard of care</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Outcomes listed in Table 1</td>
</tr>
</tbody>
</table>
| Study design      | 2021 Guideline: RCTs and observational studies  
2023 Guideline: RCTs published in peer-reviewed journals |
<p>| Cochrane systematic reviews | None relevant |
| SoF tables        | Supplementary Table S4 |
| Clinical question | In patients with nonproliferative (Class I, II, V, or VI) LN, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve efficacy outcomes and reduce adverse effects? |
| Population        | Patients with biopsy-proven nonproliferative (Class I, II, V, or VI) LN |
| Intervention      | Immunosuppressive therapy |
| Comparator        | No treatment, placebo, or other immunosuppressive therapies |
| Outcomes          | Outcomes listed in Table 1 |
| Study design      | RCTs |
| Cochrane systematic reviews | None relevant |
| SoF tables        | Supplementary Tables S29–S31 |
| Clinical question | In patients with biopsy-proven proliferative (Class III, IV, III/V, or IV/V) LN, what immunosuppressive agents, compared to no treatment, placebo, or other immunosuppressive therapies, improve clinical efficacy outcomes and reduce adverse effects? |
| Population        | Patients with biopsy-proven proliferative (Class III, IV, III/V, or IV/V) LN |
| Intervention      | Immunosuppressive therapy |
| Comparator        | No treatment, placebo, or other immunosuppressive therapies |
| Outcomes          | Outcomes listed in Table 1 |
| Study design      | RCTs |</p>
<table>
<thead>
<tr>
<th>Cochrane systematic reviews</th>
<th>Tunnicliffe DJ, et al. Immunosuppressive treatment for proliferative lupus nephritis. Cochrane Database of Systematic Reviews. 2018;6;CD002922718</th>
</tr>
</thead>
<tbody>
<tr>
<td>SoF tables</td>
<td>Supplementary Tables S5–S28, S32–S50</td>
</tr>
</tbody>
</table>

LN, lupus nephritis; MCD, minimal change disease; PICOM, Population, Intervention, Comparator, Outcomes, Methods; RCT, randomized controlled trial; SoF, summary of findings
Literature searches and article selection. For the KDIGO 2023 Clinical Practice Guideline for the Management of Lupus Nephritis, updated literature searches were conducted in MEDLINE (via Pubmed), Embase, and the Cochrane Central Register of Controlled Trials. The searches were restricted to records entered into the databases since January 1, 2020. This was done to provide a 6-month overlap with the prior searches. The searches were conducted on July 7, 2022.

The titles and abstracts resulting from the searches were screened by 2 members of the ERT who independently assessed retrieved abstracts, and if necessary, the full text, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion with a third member of the ERT.

For the KDIGO 2021 guideline, a total of 25,925 citations were screened. Of these, 479 RCTs and 102 observational studies were included in the evidence review for all diseases (Figure 14). For the 2023 update, a total of 1103 citations were screened. From these, we found 18 new eligible articles on lupus nephritis that addressed 15 new RCTs and 2 new analyses of previously included RCTs.

![Figure 14. Search yield and study flow diagram.](#) *15 RCTs in 16 records and 2 new records from previously identified studies
Data extraction. For the KDIGO 2023 Clinical Practice Guideline for the Management of Lupus Nephritis, data extraction was performed by 1 member of the Brown ERT and confirmed by the 2 other members of the ERT. The Brown ERT extracted data into the forms designed by the Cochrane ERT. The Cochrane ERT designed data extraction forms to capture data on study design, study participant characteristics, intervention and comparator characteristics, and critical and important outcomes. Any differences in extraction between members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Critical appraisal of studies. The majority of reviews undertaken were intervention reviews that included RCTs. For these reviews, the Cochrane Risk of Bias tool was used to assess individual study limitations based on the following items:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
- Participants and personnel (performance bias)
- Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

All critical appraisal was conducted independently by 2 members of the ERT, with disagreements regarding the risk of bias adjudications resolved by consultation with a third review author.

Evidence synthesis and meta-analysis. Measures of treatment effect. Dichotomous outcome (all-cause mortality, kidney failure, ≥50% loss of GFR, infection, malignancy, complete remission/relapse) results were expressed as RR with 95% CI. When continuous scales of measurement were used to assess the effects of treatment, such as annual GFR loss, the mean difference (MD) with 95% CI was used.

Data synthesis. Data were pooled using the Mantel-Haenszel random-effects model for dichotomous outcomes and the inverse variance random-effects model for continuous outcomes. The random-effects model was chosen because it provides a conservative estimate of effect in the presence of known and unknown heterogeneity.

Assessment of heterogeneity. Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes, and of risk ratios, and by χ² tests. A P value of <0.1 was used to denote statistical heterogeneity, and an I² was calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance. We used conventions of interpretation as defined by Higgins et al.

Assessment of publication bias. We made every attempt to minimize publication bias by including unpublished studies (for example, by searching online trial registries). To assess publication bias, we used funnel plots of the log odds ratio (effect vs. standard error of the effect size) when a
sufficient number of studies were available (i.e., >10 studies). Other reasons for the asymmetry of funnel plots were considered.

**Subgroup analysis and investigation of heterogeneity.** Subgroup analysis was undertaken to explore whether there were clinical differences among the studies that may have systematically influenced the differences that were observed in the critical and important outcomes. However, subgroup analyses are hypothesis-forming rather than hypothesis-testing and should be interpreted with caution. The following subgroups were considered: baseline kidney function (GFR, proteinuria, presence of albuminuria, presence of macroscopic hematuria), histopathologic class of disease, primary versus secondary forms of disease, sex, and adult versus pediatric. The test of subgroup differences used the $I^2$ statistic and a $P$ value of 0.10 (noting that this is a weak test).

**Sensitivity analysis.** The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis, taking account of the risk of bias, as specified
- Repeating the analysis excluding any very long or large studies, to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry vs. other), and country in which the study was conducted.

However, the available data were insufficient to determine the influence of these factors on the effect size of critical and important outcomes.

**Grading the quality of the evidence and the strength of a guideline recommendation.** GRADING the quality of the evidence for each outcome across studies. The overall quality of the evidence related to each critical and important outcome was assessed using the GRADE approach, which assesses the quality of the evidence for each outcome. For outcomes that are based on data from RCTs, the initial grade for the quality of the evidence is considered to be high. For observational studies, the initial quality of the evidence is low. The quality of the evidence is lowered in the event of study limitations; important inconsistencies in results across studies; indirectness of the results, including uncertainty about the population, intervention, and outcomes measured in trials and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, data were benchmarked against optimal information size, low event rates in either arm, CIs that indicate appreciable benefit and harm (25% decrease and 25% increase in the outcome of interest), and sparse data (only 1 study), all indicating concerns about the precision of the results. The final grade for the quality of the evidence for an outcome could be high, moderate, low, or very low (Table 3). For observational studies and other study types, it is possible for the quality of the evidence to be upgraded from a rating of low quality, according to the specified criteria. For further details on the GRADE approach for rating quality of the evidence, see Table 4.
Table 3 | Classification for certainty of the evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Certainty of evidence</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effect is close to the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>The estimate of the effect is very uncertain, and often it will be far from the true effect.</td>
</tr>
</tbody>
</table>

Table 4 | GRADE system for grading certainty of evidence

<table>
<thead>
<tr>
<th>Study design</th>
<th>Starting grade for the quality of evidence</th>
<th>Step 2—Lower grade</th>
<th>Step 3—Raise grade for observational evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs</td>
<td>High</td>
<td>Study limitations: –1, serious –2, very serious</td>
<td>Strength of association +1, large effect size (e.g., &lt;0.5 or &gt;2) +2, very large effect size (e.g., &lt;0.2 or &gt;5)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Inconsistency: –1, serious –2, very serious</td>
<td></td>
</tr>
<tr>
<td>Observational studies</td>
<td>Low</td>
<td>Indirectness: –1, serious –2, very serious</td>
<td>Evidence of a dose–response gradient</td>
</tr>
<tr>
<td></td>
<td>Very low</td>
<td>Imprecision: –1, serious –2, very serious</td>
<td>All plausible confounding would reduce the demonstrated effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Publication bias: –1, serious –2, very serious</td>
<td></td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; GRADE, Grading of Recommendations Assessment, Development, and Evaluation

Summary of findings (SoF) tables. The SoF tables were developed to include a description of the population, intervention, and comparator. In addition, the SoF tables included results from the data synthesis as relative and absolute effect estimates. The grading of the quality of evidence for each critical and important outcome is also provided in the SoF tables. For the 2023 update, the SoF tables were updated or created manually. The SoF tables are available in the Data Supplement: Appendix C and Appendix D (https://kdigo.org/guidelines/gd/).
Developing the recommendations. For the KDIGO 2023 Clinical Practice Guideline for the Management of Lupus Nephritis, the existing recommendations were reviewed and revised, as necessary, and new recommendations were drafted by the Work Group and Co-Chairs. Recommendations were revised in a multistep process by email and by teleconferences. The Brown ERT participated in these discussions to ensure consistency with the evidence base and to provide additional feedback.

The final draft was sent for external public review, and reviewers provided open-ended responses. Based on the external stakeholder feedback, the draft was further revised by the Work Group. All Work Group members provided feedback on initial and final drafts of the guideline statements and text and approved the final version of the guideline. The ERT also provided a descriptive summary of the evidence quality in support of the recommendations.

Grading the strength of the recommendations. The strength of a recommendation is graded as strong or weak (Table 5). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall quality of the evidence, patient values and preferences, resource use and costs, and considerations for implementation (Table 6).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td></td>
</tr>
<tr>
<td>“We recommend”</td>
<td>Most people in your situation would want the recommended course of action, and only a small proportion would not.</td>
</tr>
<tr>
<td></td>
<td>Most patients should receive the recommended course of action.</td>
</tr>
<tr>
<td></td>
<td>The recommendation can be evaluated as a candidate for developing a policy or a performance measure.</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td></td>
</tr>
<tr>
<td>“We suggest”</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not.</td>
</tr>
<tr>
<td></td>
<td>Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.</td>
</tr>
<tr>
<td></td>
<td>The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.</td>
</tr>
</tbody>
</table>
Table 6 | Determinants of the strength of recommendation

<table>
<thead>
<tr>
<th>Factors</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance of benefits and harms</td>
<td>The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is warranted.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>The higher the quality of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low quality of the evidence will warrant a strong recommendation.</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.</td>
</tr>
<tr>
<td>Resource use and costs</td>
<td>The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.</td>
</tr>
</tbody>
</table>

Balance of benefits and harms. The Work Group and ERT determined the anticipated net health benefit on the basis of expected benefits and harms across all critical and important outcomes from the underlying evidence review.

The overall quality of the evidence. The overall quality of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall quality of the evidence was graded (A, B, C, or D—Table 3).

Patient values and preferences. No patients or caregivers were involved in the Work Group. The Work Group, from their experience in managing patients with GD and their understanding of the best available scientific literature, made judgments on the values and preferences of patients. Formal qualitative evidence synthesis on patient priorities and preferences was undertaken, but there was limited evidence available to inform the formulation of guideline recommendations (Appendix D).

Resources and other costs. Healthcare and non-healthcare resources, including all inputs in the treatment management pathway, were considered in grading the strength of a recommendation. The following resources were considered: direct healthcare costs; non-healthcare resources, such as transportation and social services; informal caregiver resources (e.g., time of family and caregivers); and changes in productivity. Economic evaluations, including cost-effectiveness analysis, were not conducted for any of the guideline topics.
**Practice points.** In addition to graded recommendations, KDIGO guidelines now include “practice points” to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care, and they supplement recommendations for which a larger quantity of evidence was identified. They are issued when a clinical question was not supported by a systematic review, often to help readers implement the guidance from graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they also may be based on limited evidence. For example, practice points were provided on monitoring, frequency of testing, dosing adjustments for the stage of CKD, and use of therapies in specific subgroup populations. Practice points were sometimes formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

**Format for guideline recommendations.** Each guideline recommendation provides an assessment of the strength of the recommendation (strong, level 1; or weak, level 2) and the quality of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Quality of the evidence, Values and preferences, Resource use and costs, Considerations for implementation), and rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale may support a practice point.

**Limitations of the guideline development process.** The evidence review prioritized RCTs as the primary source of evidence. For a select number of clinical questions in this guideline, the ERT undertook a comprehensive evidence review beyond RCTs. However, these reviews were not exhaustive, as specialty or regional databases were not searched, and manual searching of journals was not performed for these reviews. In the development of these guidelines, no scoping exercise with patients, limited searches of the qualitative literature, or formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, formal economic evaluations were not undertaken for all topics.
JF reports consultancy for AstraZeneca, Calliditas, Novartis, Omeros, Otsuka, Stadapharm, and Travere; serving in the speaker bureau for Bayer and Otsuka; and serving on the advisory board for NovoNordisk and Visterra.


IMA reports funding for travel and/or accommodation from Aurinia; and serving on the advisory board for Aurinia.

TMC reports support for studies or manuscripts pertaining to this topic from Astellas, AstraZeneca, and GSK; and consultancy from GSK and Otsuka.

Z-HL declared no competing interests.

JMMV reports serving in the speaker bureau for AstraZeneca, Boehringer Ingelheim, GSK, and Roche; and serving on the advisory board for Kezar Pharmaceuticals.

KDIGO Chairs

MJ reports consultancy for Astellas*, AstraZeneca*, Bayer*, Boehringer-Ingelheim*, CSL Vifor*, Fresenius Medical Care Asia Pacific*, GSK*, and Mundipharma*; grants /research support from Amgen* and AstraZeneca*; being in the speaker bureau for Astellas*, AstraZeneca*, Bayer*, Boehringer-Ingelheim*, CSL Vifor, and Mundipharma*.

*Monies paid to institution.
WCW reports consultancy for Akebia/Otsuka, AstraZeneca, Bayer, Boehringer Ingelheim/Lilly, and Zydus.

METHODS Chair

MT has received honoraria from AstraZeneca*.
*Monies donated to charity

Evidence Review Team

EMB declared no competing interests.

GA declared no competing interests.

CEG reports consultancy for Alexion; serving in the speaker bureau for Alexion; and funding for travel and/or accommodation from Alexion.
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