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KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

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TABLES

FIGURES

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

KDIGO EXECUTIVE COMMITTEE

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 certainty of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade	**Patients**	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	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.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

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

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.

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

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

	Conventional unit	Conversion factor	SI unit
Albumin	g/dl	10	g/l
Creatinine	mg/dl	88.4	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Cyclosporine	ng/ml	0.832	nmol/l
Mycophenolic acid	μg/ml	3.12	μmol/l
Protein-creatinine ratio (PCR)	mg/g	0.113	mg/mmol
Tacrolimus	ng/ml	1.24	nmol/l

PCR, protein-creatinine ratio; SI, International System of Units.
Note: Conventional unit × conversion factor = SI unit.

RELATIONSHIP AMONG CATEGORIES FOR ALBUMINURIA AND PROTEINURIA

	Categories		
Measure	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/d)	<30	30–300	>300
PER (mg/d)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; PCR, protein–creatinine ratio; PER, protein excretion rate.
Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race, and diet; therefore, the relationship among these categories is approximate only. The relationship between urine reagent strip results and other measures depends on urine concentration.

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 deoxyribonucleic acid
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[s])
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 and updated in April 2023. 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.

Foreword

Kidney International (2024) **105** (Suppl 1S), S1–S69; https://doi.org/10.1016/j.kint.2023.09.002

The mission of Kidney Disease: Improving Global Outcomes (KDIGO) is to "improve the care and outcomes of people with kidney disease worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines." Since its inception in 2003, KDIGO has published comprehensive guidelines on many distinct topics, including the Clinical Practice Guidelines for the Management of Glomerulonephritis in 2012 and Glomerular Diseases in 2021. The latter guideline summarized recommendations for 11 diseases based on evidence available through June 2020. The current update, just 2 years later, reflects the unprecedented pace of scientific discovery in the field, and centers on guidance regarding the diagnosis, treatment, and monitoring of kidney involvement in systemic lupus erythematosus.

KDIGO strives to maintain the highest standards of excellence and provide clinicians with the most relevant, evidence-based guidance, incorporating both recent advancements as well as widely accepted clinical standards. As such, this Lupus nephritis guideline update features a combination of both graded recommendations and practice points. Graded recommendations are based on a systematic review of the evidence and are graded for strength of the recommendation (level 1, "we recommend" or level 2, "we suggest") and certainty of the evidence (A, "high"; B, "moderate"; C, "low"; or D, "very low"). Practice points are ungraded, consensus-based statements representing the expert judgment of the Work Group. These practice points are issued when there has not been a systematic review. Some practice points aim at helping the reader in the implementation of graded recommendations and we often provide these in a graphical format. Readers should consider practice points as expert guidance or "good practice statements" and use them as they see fit to inform the care of patients.

We once again thank Jürgen Floege, MD, and Brad H. Rovin, MD, for leading this important initiative, and we very much appreciate the continued dedication of the Work Group members, Tak Mao (T.M.) Chan, MD, DSc; Isabelle Ayoub, MD; Zhi-Hong Liu, MD; and Juan Mejía-Vilet, MD, PhD. Each of these volunteers provided a considerable amount of time and expertise to the current Lupus nephritis guideline. The independent Evidence Review Team (ERT) from Brown University School of Public Health led by Ethan Balk, MD, MPH, and Craig Gordon, MD, MS, updated the evidence reviews that informed this latest version of the guideline.

To ensure transparency and rigorous public review during guideline development, the draft guideline update was made publicly available for comment in March 2023, per KDIGO policy. We very much appreciate the feedback received from the scientific community. All Work Group members have revised and approved the update for formal release.

In summary, we are pleased to present this revised Clinical Practice Guideline for the Management of Lupus Nephritis, reflecting the most recent and up-to-date global evidence for the care of people with lupus nephritis throughout the world. We are thrilled at the pace of scientific advancement and are exceptionally grateful to the Work Group Co-Chairs, Work Group members, and other contributors to this very important KDIGO activity.

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Abstract

The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline for the Management of Lupus Nephritis represents a focused update of the Lupus nephritis chapter 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 focused on guidance related to treatment of lupus nephritis. 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 strength of recommendations and certainty of the evidence following the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. Limitations of the evidence are discussed and areas of future research are presented.

Keywords: evidence-based; glomerular diseases; glomerulonephritis; guideline; KDIGO; lupus nephritis; nephrotic syndrome; systematic review

CITATION

In citing this document, the following format should be used: Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis. *Kidney Int.* 2024;105(1S):S1–S69.

Summary of recommendation statements and practice points

10.1 Diagnosis

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

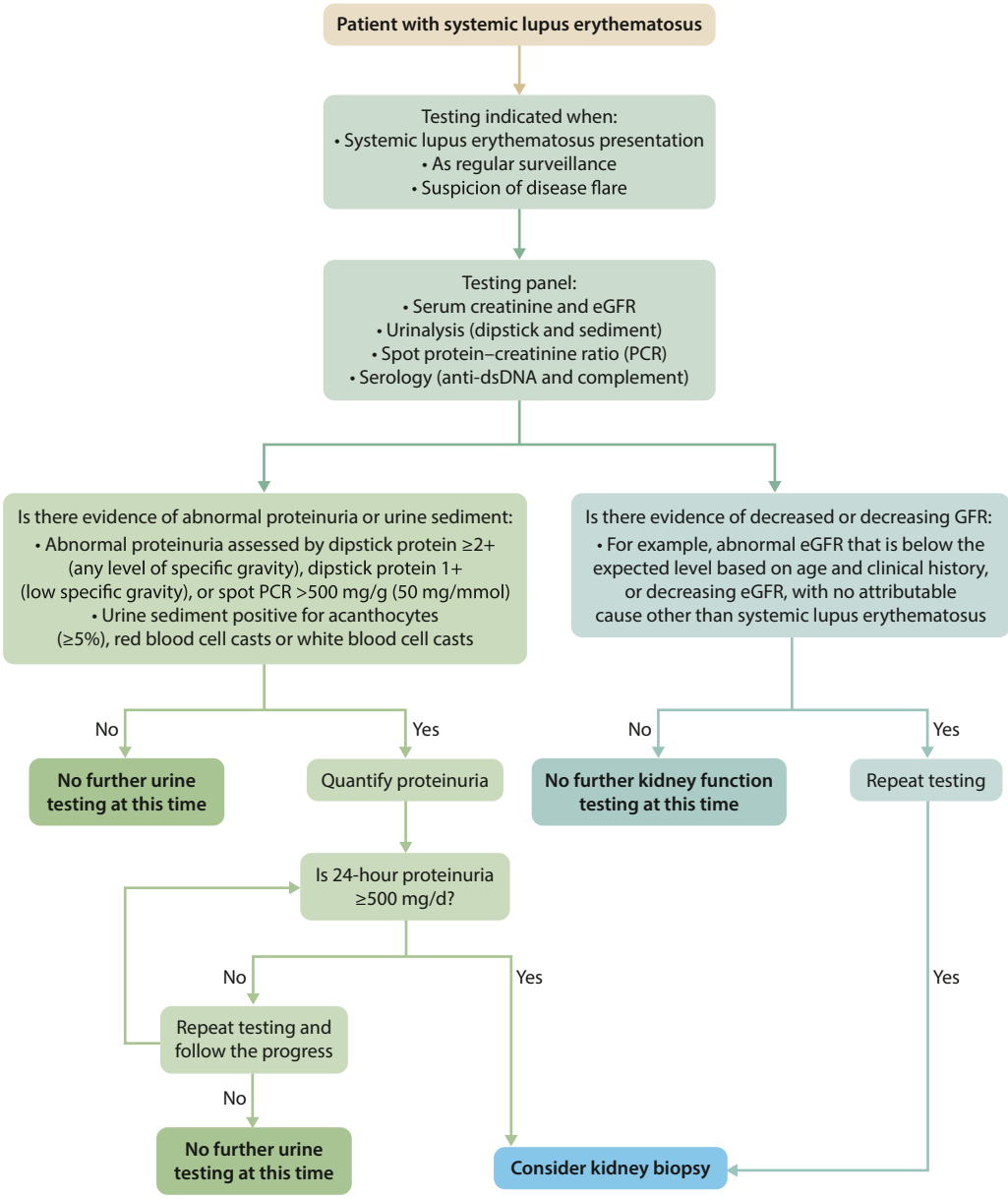

Figure 1 | Diagnosis of kidney involvement in systemic lupus erythematosus. anti-dsDNA, anti-double-stranded deoxyribonucleic acid; eGFR, estimated glomerular filtration rate.

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 contra-indicated *(1C)*.

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

Figure 3 | Measures to minimize the risk of complications related to lupus nephritis or its treatment. Note: Chapter 1 refers to Chapter 1 of the KDIGO Guideline on Glomerular Diseases. AKI, acute kidney injury; CKD, chronic kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RAAS, renin–angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter-2.

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.

10.2.2 Class I or Class II lupus nephritis

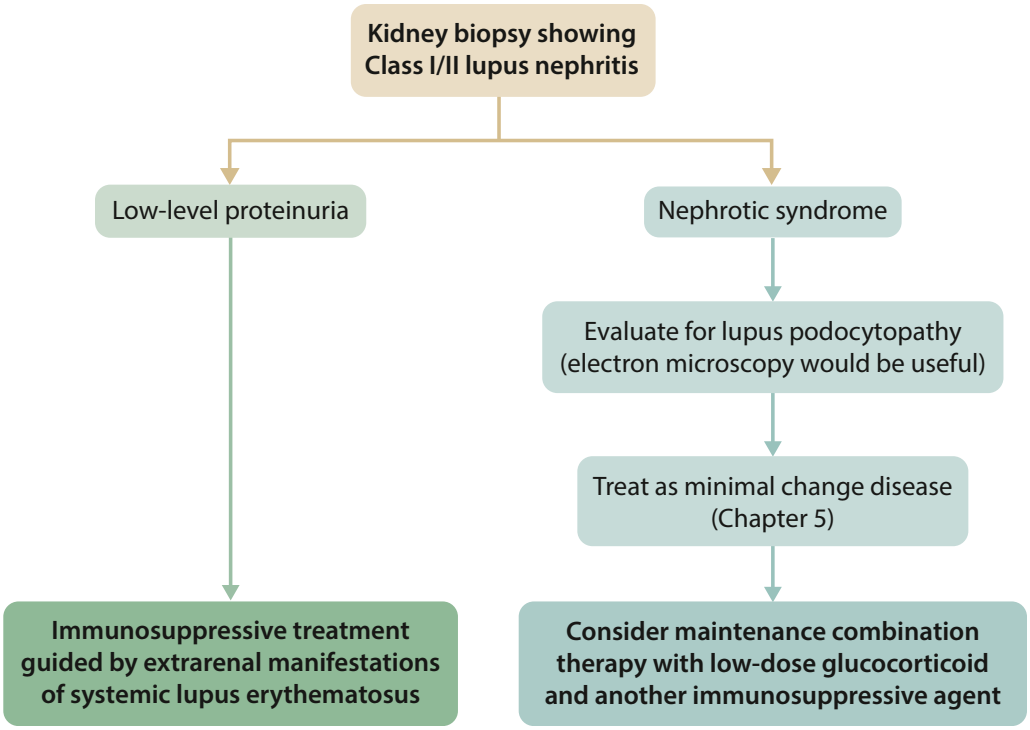

Figure 4 | Immunosuppressive treatment for patients with Class I or Class II lupus nephritis. Note: Chapter 5 refers to Chapter 5 of the KDIGO Guideline on Glomerular Diseases.

Practice Point 10.2.2.1: Approach to immunosuppressive treatment for patients with Class I or Class II LN (Figure 4)

10.2.3 Class III or Class IV lupus nephritis

10.2.3.1 Initial therapy of active Class III/IV lupus nephritis

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus any *one* of the following:
i. mycophenolic acid analogs (MPAA) (*1B*); or
ii. low-dose intravenous cyclophosphamide (*1B*); or
iii. belimumab and either MPAA or low-dose intravenous cyclophosphamide (*1B*); or
iv. MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (i.e., estimated glomerular filtration rate [eGFR] ≤45 ml/min per 1.73 m^2) (*1B*).

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

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

Figure 7 | Examples of glucocorticoid regimens for lupus nephritis. max, maximum.

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

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

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

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

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

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

10.2.3.2 Maintenance therapy for Class III and Class IV lupus nephritis

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

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

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

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

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

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

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).

Maintenance immunosuppressive regimens	Low-dose glucocorticoids AND					
	Mycophenolic acid analogs	Azathioprine	Belimumab and mycophenolic acid analogs or azathioprine	CNI and mycophenolic acid analogs	CNI (such as voclosporin, tacrolimus or cyclosporine)	Mizoribine
Comments	Preferred treatment based on high-certainty evidence; lower flare rate than azathioprine maintenance	Low medication cost; safe in pregnancy	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]	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]	Tacrolimus and cyclosporine safe in pregnancy; insufficient pregnancy data on voclosporin	Experience mostly in Japanese patients

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

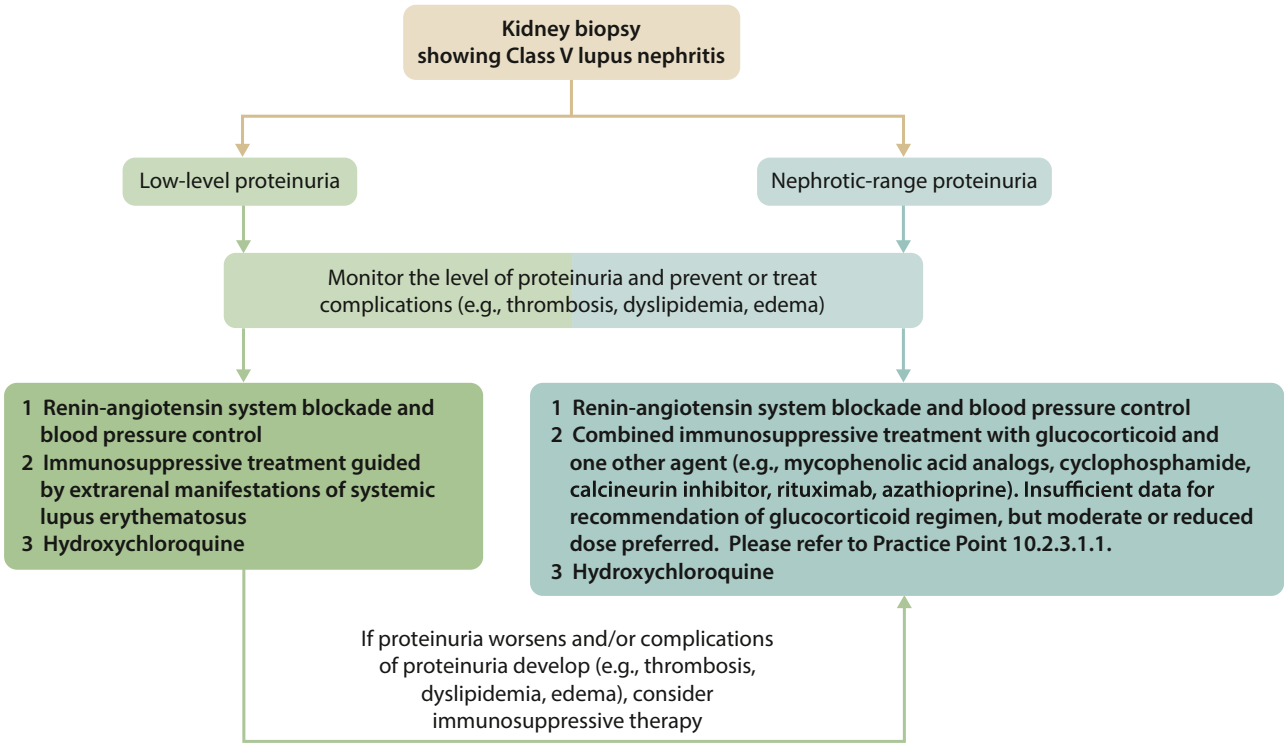

Figure 10| Management of patients with pure Class V lupus nephritis.

10.2.5 Response and relapse considerations

10.2.5.1 Assessing treatment response in LN

Practice Point 10.2.5.1.1: Definitions of response to therapy in LN used in clinical trials are provided in Figure 11.

Criteria	Definition
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
Primary efficacy renal response	• PCR ≤0.7 g/g (70 mg/mmol) • eGFR that was no worse than 20% below the pre-flare value or ≥60 ml/min per 1.73 m^2 • No use of rescue therapy for treatment failure
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • 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 | Definitions of response commonly used in clinical trials of lupus nephritis. *For children <18 years old, complete response is defined as proteinuria <0.5 g/1.73 m^2 per day or <300 mg/m^2 per day based on a 24-hour urine specimen. eGFR, estimated glomerular filtration rate; PCR, protein–creatinine ratio.

10.2.5.2 Management of unsatisfactory response to treatment

Practice Point 10.2.5.2.1: An algorithmic approach to patients whose response to therapy is deemed unsatisfactory is provided in Figure 12.

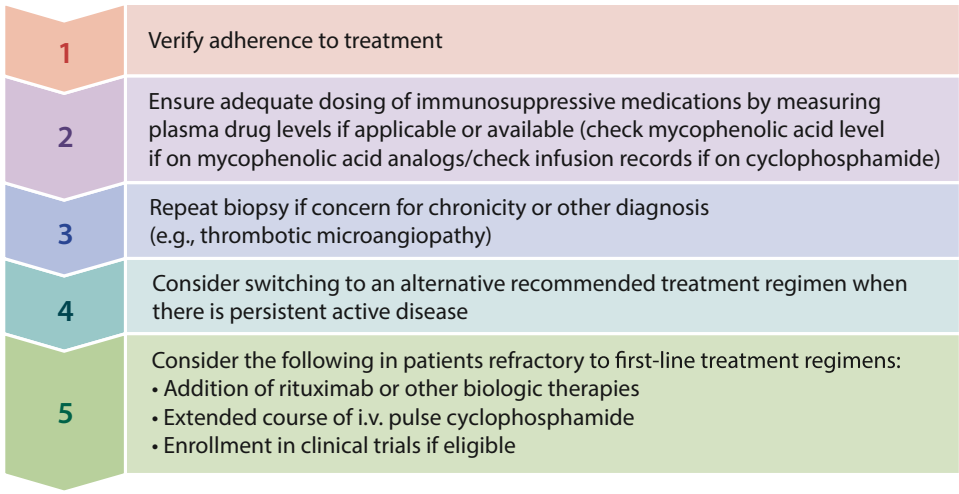

Figure 12 | Management of patients who show unsatisfactory response to initial therapy for active lupus nephritis. i.v., intravenous.

10.2.5.3 Treatment of LN relapse

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

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 13.[1]

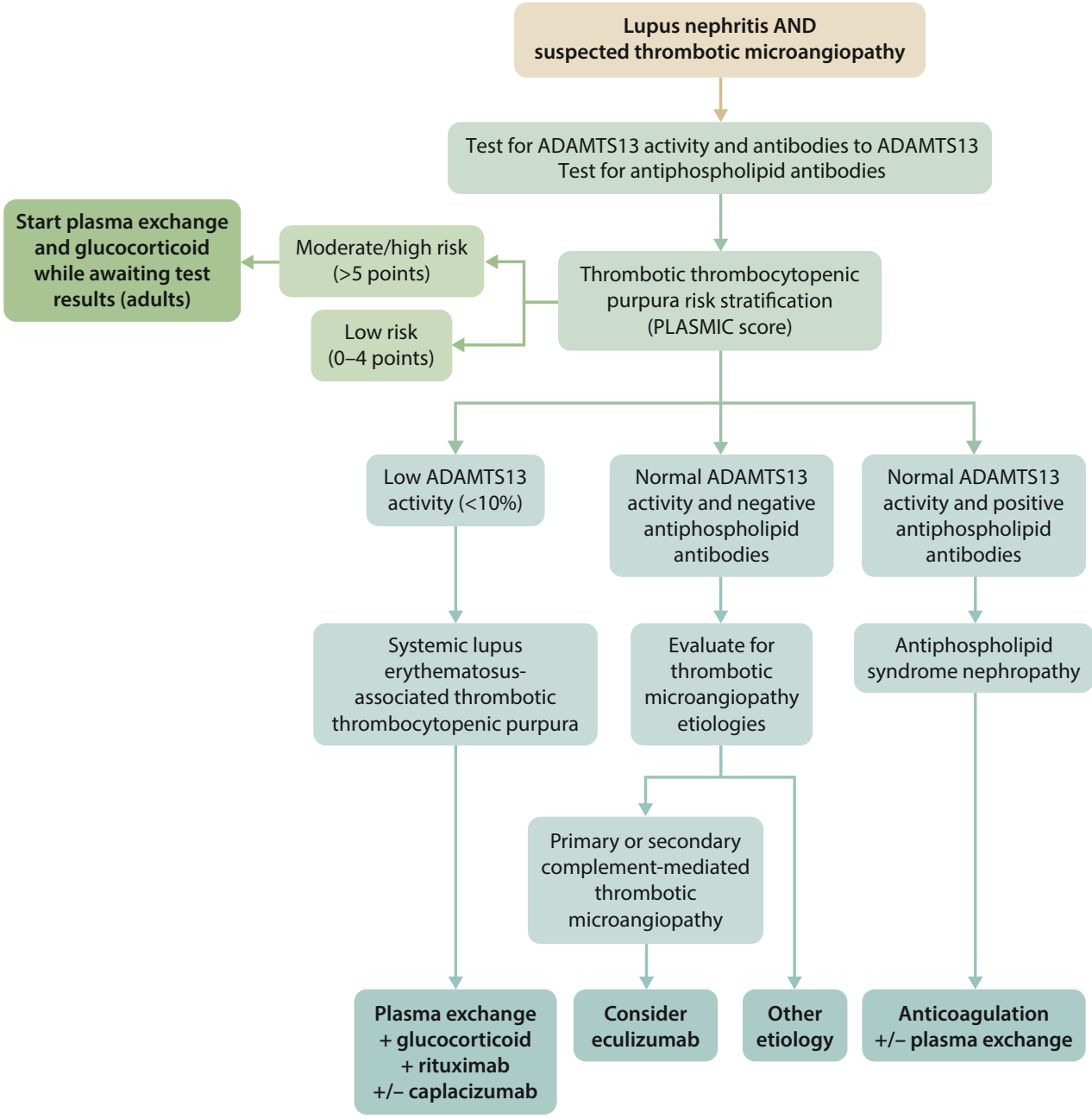

Figure 13 | Management of patients with lupus nephritis and thrombotic microangiopathy (TMA). Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol*. 2017;4:e157–e164.[1] ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PLASMIC, Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem-cell or solid-organ transplant, mean corpuscular volume (MCV), international normalized ratio (INR), Creatinine.

10.3.2 Pregnancy in patients with lupus nephritis

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

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

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

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.

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.[2–5] Kidney involvement in SLE has been associated with higher mortality, especially for patients progressing to kidney failure.[6–8] 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 10.3.3.1.

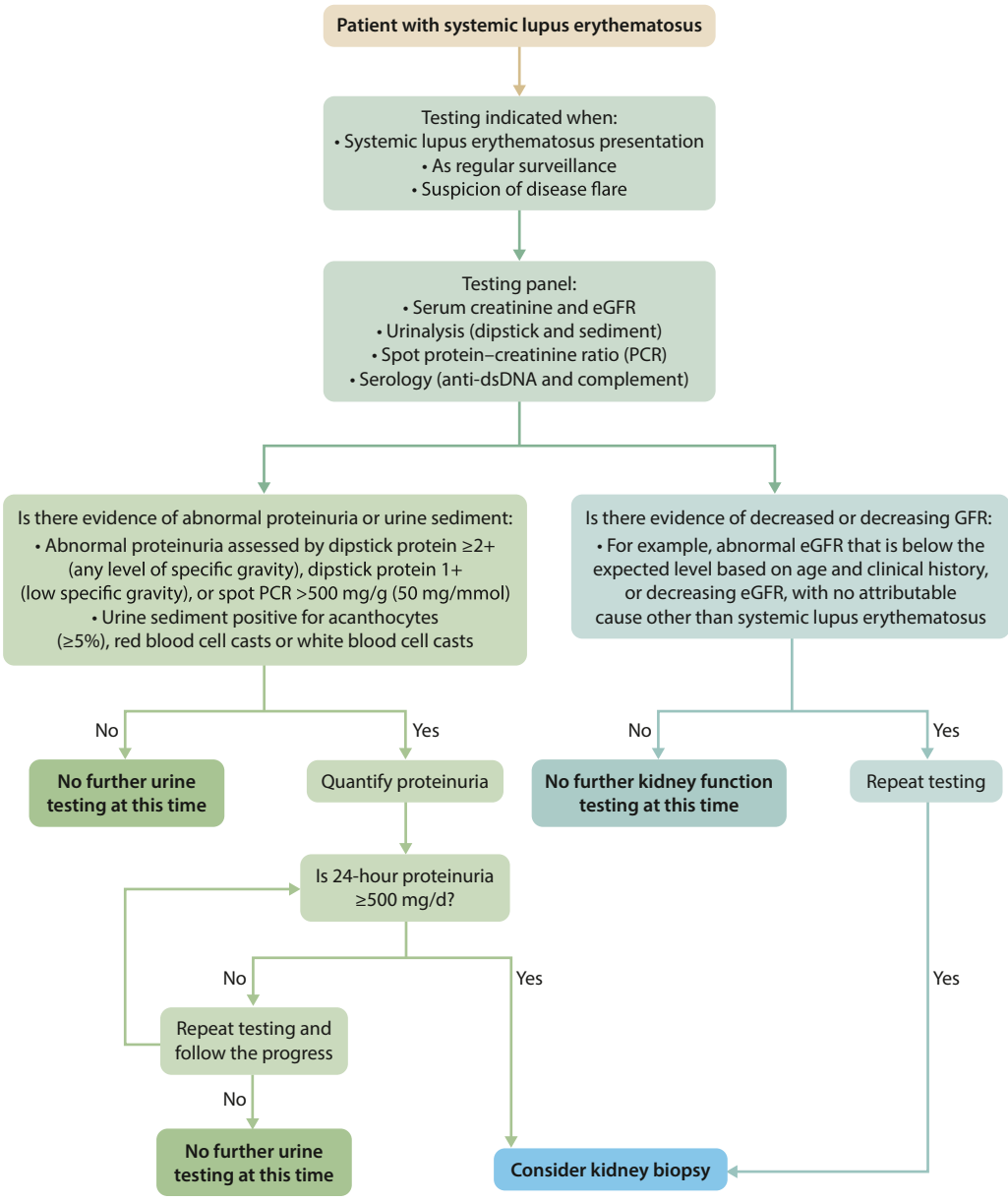

Figure 1 | Diagnosis of kidney involvement in systemic lupus erythematosus. anti-dsDNA, anti-double-stranded deoxyribonucleic acid; eGFR, estimated glomerular filtration rate.

10.1 Diagnosis

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

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,[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.[10–20] Kidney biopsies should be read by an experienced kidney pathologist and classified according to the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) scheme.[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).

Components of the activity index	Score	Calculating the activity score Extent of lesion	Points
• Endocapillary hypercellularity	0–3	Not present	0
• Neutrophils and/or karyorrhexis	0–3	Present in <25%	1
• Fibrinoid necrosis	(0–3) × 2	Present in 25%–50%	2
• Hyaline deposits (wire loop and/or hyaline thrombi)	0–3	Present in >50%	3
• Cellular/fibrocellular crescents	(0–3) × 2		
• Interstitial inflammation (interstitial leukocytes)	0–3		
	Total: 0–24		
Items included in the NIH chronicity score	**Score**	**Calculating the chronicity score** **Extent of lesion**	**Points**
• Total glomerulosclerosis (global + segmental)	0–3	Present in <10%	0
• Fibrous crescents	0–3	Present in 10%–25%	1
• Interstitial fibrosis	0–3	Present in 25%–50%	2
• Tubular atrophy	0–3	Present in >50%	3
	Total: 0–12		
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 randomized controlled trial (RCT) data.

Key information

Balance of benefits and harms. The reported benefits of antimalarial use in SLE include lower flare rates (including kidney),[24,25] higher response rates to therapy,[24–27] slower progression of kidney disease,[28,29] lower incidence of cardiovascular (CV) and thrombotic events in patients with antiphospholipid antibodies,[30–33] less organ damage,[28,34–38] improved lipid profile,[39,40] and better preservation of bone mass.[41]

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.[42–44] 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.[45,46]

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 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.[47] 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.[48] Low-certainty observational studies have indicated that hydroxychloroquine may have kidney benefits, may have 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 (Supplementary Table S4[26–28,36–50]). 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 (Supplementary Table S4[28,50]).

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. In low-resource settings, one might consider substituting it with structurally similar drugs such as chloroquine that have a similar mechanism of action and are less expensive, but the increased risk of toxicity of the latter should be noted.

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 the 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 m^2; 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 5 mg/kg/d ($\leq$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] Recent data suggested that a blood hydroxychloroquine level above 0.6 mg/l may be associated with a lower risk of LN flare.[55] In patients with eGFR <30 ml/min per 1.73 m^2, the dose of hydroxychloroquine should be reduced by $\geq 25\%$. 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.

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.[56,57] Infections, cardiovascular (CV) complications, and CKD, especially kidney failure, are major causes of death.[6–8,58] Early deaths are related to infections or lupus activity, while CV and malignant complications and deaths related to kidney failure account for late mortalities.[59]

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

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

Figure 3 | Measures to minimize the risk of complications related to lupus nephritis or its treatment. Note: Chapter 1 refers to Chapter 1 of the KDIGO Guideline on Glomerular Diseases. AKI, acute kidney injury; CKD, chronic kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RAAS, renin–angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter-2.

(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.[60]

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.[49,56,61] 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.[61] Avoidance of overimmunosuppression is an important measure to reduce the risk of infections and adverse outcomes. 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. 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.[2,62] 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.[63] 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.[64] However, a recent retrospective study from Japan reported an adverse drug reaction 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.[65] Pentamidine inhalation can be used in patients who are not suitable for TMP-SMX. Alternative second-line agents include dapsone and atovaquone.

Response to vaccination is reduced following exposure to high-dose immunosuppression with glucocorticoid, mycophenolate, or rituximab.[66] Vaccination for the prevention of hepatitis B infection is recommended, especially in endemic regions. The rate of *Herpes zoster* is 2–10 times higher in patients with SLE than in healthy controls. 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. While some guidelines recommend the use of recombinant zoster vaccine in immunodeficient or immunosuppressed patients, including patients with SLE, there are controversial data on whether the vaccine might precipitate a flare of immune-mediated diseases in a small number of patients, and a study investigating its efficacy and safety in patients with SLE is ongoing. There is also concern that the polio vaccination has been associated with lupus flares, whereas the data on influenza vaccination are conflicting. Vaccination against SARS-CoV-2 is recommended in general, although there have been anecdotal reports of new onset or flares of immune-mediated diseases following exposure to mRNA COVID-19 vaccines.[67]

CKD progression. CKD is common in patients with LN due to the kidney flares that reduce nephron mass.[68,69] In addition to treatment and prevention of active LN, it is important that measures to reduce the rate of kidney function deterioration be included as part of holistic management, such as optimal blood pressure control, the use of renoprotective medications, avoidance of nephrotoxic insults, and prevention of circumstances that may result in acute kidney injury (AKI).

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. The choice of methods for contraception should be discussed, and if necessary, the opinion of a gynecologist should be sought. For patients who prefer oral hormonal contraception, estrogen–progestin contraceptives with ethinyl estradiol dose 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.[70] Data from women exposed to chemotherapy showed efficacy of gonadotrophin-releasing hormone (GnRH) analogs in reducing the rate of premature ovarian failure, whereas the putative gonadal protective effect of oral contraceptive pills appeared variable.[71] 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.[72,73] In children, glucocorticoid cumulative dose affects peak bone mass and growth.[74] Individual evaluation of fracture risk can be estimated using patient demographics and clinical history, glucocorticoid dose, and the Fracture Risk Assessment Tool (FRAX) score.[75,76] 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.[77,78]

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.[79,80] 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.[81] Although there is evidence showing efficacy and safety of human papillomavirus vaccines in patients with SLE, the development of SLE or lupus-like disease following vaccination has been reported.[82,83]

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)

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.[84]

Patients with Class I or II histology but with nephrotic-range proteinuria or nephrotic syndrome (NS) are considered to have lupus podocytopathy. This diagnosis may be confirmed by demonstrating diffuse podocyte effacement on electron microscopy. Clinical and histologic manifestations of patients with podocytopathy are similar to those with minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), and they often show a good response to glucocorticoid treatment.[85–87] 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.[85,88–92] Data on relapse are even more limited, but there appears to be a significant risk of relapse after glucocorticoids are tapered.[93] Although optimal duration is not known, maintenance with low-dose glucocorticoid plus an additional agent such as mycophenolic acid analogs (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 any *one* of the following:

i. mycophenolic acid analogs (MPAAs) *(1B)*; or
ii. low-dose intravenous cyclophosphamide *(1B)*; or
iii. belimumab and either MPAA or low-dose intravenous cyclophosphamide *(1B)*; or
iv. MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (i.e., estimated glomerular filtration rate [eGFR] ≤45 ml/min per 1.73 m^2) *(1B)*.

This recommendation places a high value on results from clinical trials demonstrating clinical efficacy with combined immunosuppressive regimens that include glucocorticoids and either low-dose intravenous cyclophosphamide or MPAA (dual immunosuppressive therapy), as well as triple immunosuppressive regimens that include belimumab or voclosporin (or tacrolimus)

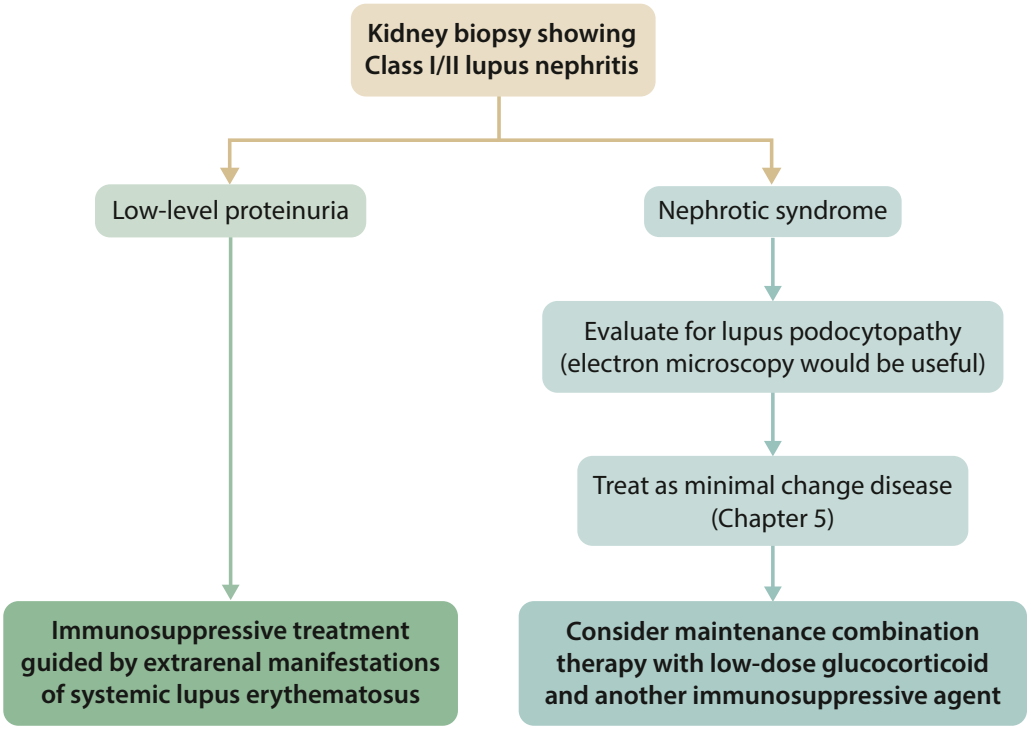

Figure 4 | Immunosuppressive treatment for patients with Class I or Class II lupus nephritis. Note: Chapter 5 refers to Chapter 5 of the KDIGO Guideline on Glomerular Diseases.

added to the above dual immunosuppression. 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. A summary of options of initial therapy that can be recommended for active proliferative LN is shown in Figure 5. The Work Group acknowledges the considerable variation of characteristics among patients. Readers are advised to refer to the practice points for discussions on the preferred choice of therapy according to patient characteristics. Also, regarding the choice of therapy and the dose of specific medications, the Work Group emphasizes the importance of preventing potential adverse effects that could result from high-dose glucocorticoid, high-dose cyclophosphamide, and CNI nephrotoxicity. In this regard, patients with CKD G3b–G5 were often excluded from the respective clinical trials.

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.[94] 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.[13,95–98] 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 aimed to improve the risk–benefit ratio of treatment. A study of 90 patients of European descent with active LN showed that, when compared to 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.[17,99] In a short-term trial that included 100 patients from India, reduced-dose cyclophosphamide showed similar efficacy to that of MPAA when both were combined with glucocorticoids.[100] 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 6 shows the details of cyclophosphamide-dosing regimens.

Following establishment of efficacy in preventing organ transplant rejection, MPAA were investigated in LN and was shown to have efficacy similar to that of cyclophosphamide in treating active LN.[100,101] 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 that of cyclophosphamide in clinical trials with MMF dose of 3 g/d, suggesting a dose effect and possible racial or ethnic variation in tolerability of MPAA. Also, concomitant high-dose glucocorticoids contributed to many treatment-associated adverse events.[12,14,100–102] 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.[19,103–105] A prospective study including 40 LN (Class IV ± V) patients from China demonstrated higher 24-week response rates in patients treated with the "multitarget" regimen compared with high-dose cyclophosphamide and glucocorticoids.[103] These findings were later corroborated in a trial of 368 Chinese patients with active LN and baseline serum creatinine (SCr) ≤3 mg/dl (265 μmol/l; translating to an eGFR level of around 25 ml/min per 1.73 m^2), showing a higher complete response rate at 6 months in the triple immunosuppressive scheme than with cyclophosphamide, though with numerically higher numbers of adverse events.[19] 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.[106]

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 m^2.[107,108] The response rates at 24 and 52 weeks were higher in voclosporin-treated groups compared with placebo, with all patients receiving 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.[109] 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).[110] 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. The 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.

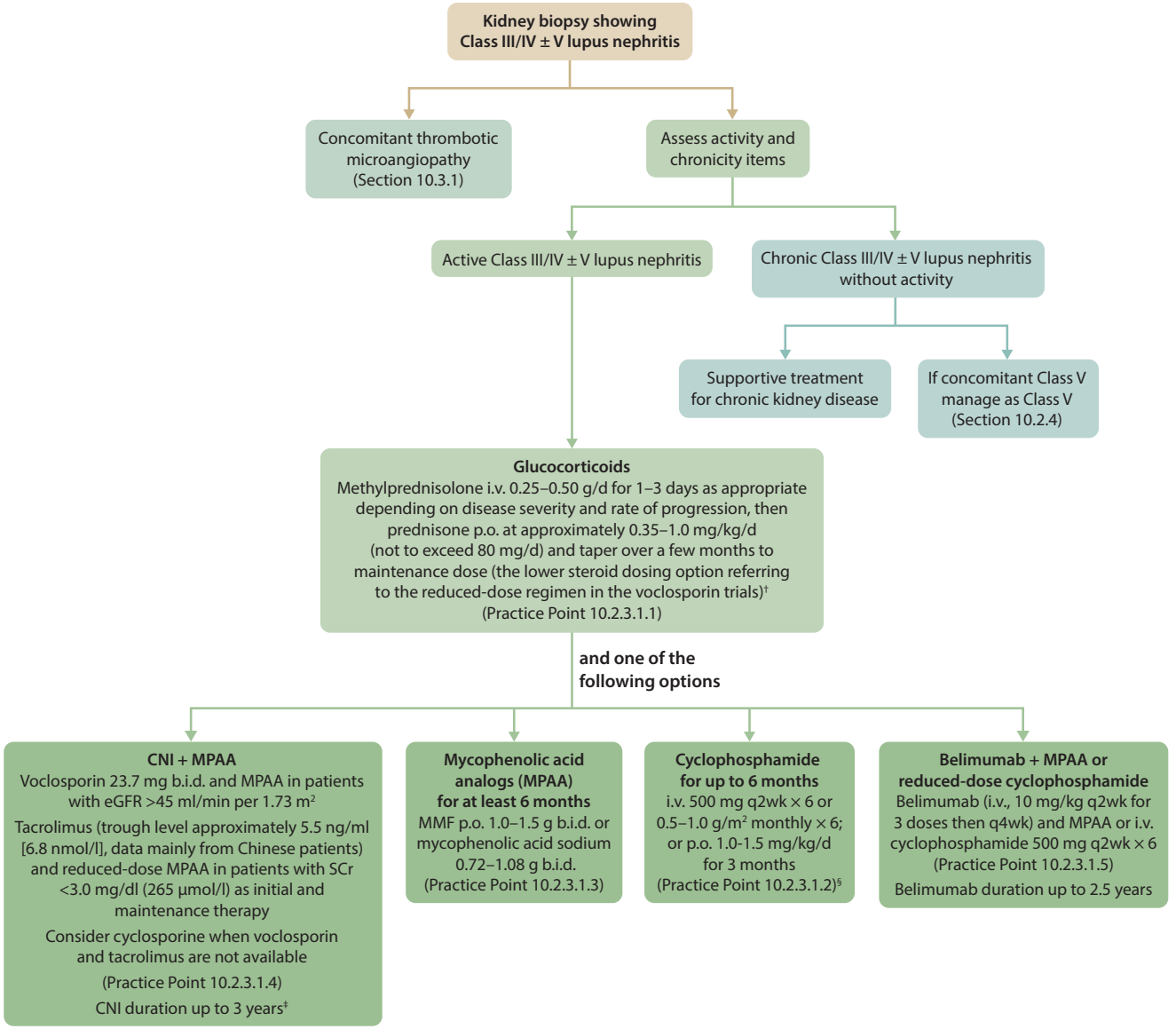

Figure 5 | Recommended approach for initial therapy of active Class III/IV lupus nephritis. Caution is warranted when calcineurin inhibitors (CNI) are used in patients with significantly impaired kidney function, in view of increased susceptibility for severe consequences due to CNI nephrotoxicity. The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

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

Figure 6| 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.

Abnormal B lymphocyte hyperreactivity is a characteristic feature in the pathogenesis of SLE. B-cell–activating factor (BAFF, also known as B lymphocyte stimulator or BLyS) is a cytokine expressed in cells with B-cell lineage and acts as a potent B cell activator. Belimumab, a human monoclonal antibody that inhibits BAFF, was approved by the 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.[111] Patients treated with belimumab had superior primary efficacy renal response rate (PERR, a composite endpoint with proteinuria ≤0.7 g/g [70 mg/mmol]) compared to placebo, while all patients received standard dual immunosuppression. The 2 groups showed similar rates of adverse events. Results from a secondary analysis and an 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.[112,113] Subgroup analysis of 142 East Asian patients showed similar findings.[114] 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 that showed similar exposure between the 2 administration routes with a higher trough level when given subcutaneously.

It is important to note that, while there were 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 are relatively scarce for the other regimens, especially for the more recent treatments such as CNI and belimumab.[96,97] 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.[15,99,115–118]

In summary, Class III and Class IV LN are severe diseases that result in AKI 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[13,95,96,101,119–121]).

High-dose versus low-dose cyclophosphamide has been compared in a few RCTs (Supplementary Table S6[17,121–124]). The results from these trials indicate that low-dose cyclophosphamide is associated with fewer adverse events (such as infection, malignancy, leukopenia, and bone toxicity[121]; 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[12,100–102,121,125–128]).

There is low-certainty evidence that triple immunosuppressive regimens that include tacrolimus, reduced-dose MPAA, and glucocorticoids are superior to standard-of-care regimens when used as initial therapy, with similar incidence of adverse events (Supplementary Table S8[19,103,104,121]). 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[107,108,129] and Supplementary Table S10[19,103,104,107,108]). 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[19,103,104,107,108]).

There is moderate-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[111,113,130]).

Values and preferences. Without treatment, the prognosis for kidney survival in patients with proliferative LN is poor. Well-informed patients with Class III and IV LN would normally choose to be treated with one of the immunosuppressive regimens with proven efficacy as outlined previously, and patients should be informed of the severe risk of declining or not adhering to treatment. Given the risks of infertility associated with cyclophosphamide and the spectra of potential malignancies, 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 high-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.[17]

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 ≤45 ml/min per 1.73 m^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.[110] The optimal duration of CNI treatment for LN remains uncertain, and there are insufficient data on subsequent tapering or discontinuation, and 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 the 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) <3 g/g (<300 mg/mmol).[113] 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 the 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 (≥3 g/g [≥300 mg/mmol]) suggested that the estimated risk of a kidney-related event or death was lower in the belimumab group.[131] Results from the 28-week open-label extension of the BLISS-LN study showed continued increase in the proportions of patients achieving PERR or complete renal response, and no safety signal, associated with belimumab treatment.[112]

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.

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. Access to appropriate therapies is essential to prevent adverse clinical outcomes, including the high treatment cost for kidney failure. 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 lower 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.[132–134]

Addition of a third drug (CNI or belimumab) increases the costs of therapy,[135] while the potential increase in complete

response rates and prevention of renal relapses may be cost-saving.[136] Access to treatment, cost barriers, 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.

Considerations for implementation. In view of the significant treatment costs,[134,137,138] 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 and cumulative exposure. Future susceptibility to malignancies increases with higher lifetime cyclophosphamide exposure, so a detailed knowledge of prior therapies is important. Many physicians may still choose high-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,[139,140] 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.[19,106]

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. Note that there are no data on voclosporin given together with cyclophosphamide. 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.

The use of CNI in patients with severe CKD requires careful individualized consideration of risk versus potential benefit, and should be done with caution and careful monitoring, and at reduced drug exposure. Voclosporin is generally not recommended for patients with a baseline eGFR ≤45 ml/min per 1.73 m^2, and these patients were excluded from the trials.[141] Similarly, in a trial investigating the triple immunosuppressive regimen of glucocorticoids and reduced-dose MMF and fixed-dose tacrolimus in Chinese patients, patients with a baseline SCr >3 mg/dl (265 μmol/l) were excluded.[19] The overall results suggest that kidney function remained relatively stable when either voclosporin or tacrolimus was used at the reported doses in the selected populations for a duration of 2–3 years.

With regard to the duration of treatment, reduced-dose cyclophosphamide is given for 12 weeks, whereas high-dose cyclophosphamide is 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 that voclosporin treatment for 3 years was safe in patients with LN 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, whose number portends the likelihood of 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 and 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 and 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 7).

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 7).

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

Figure 7 | Examples of glucocorticoid regimens for lupus nephritis. max, maximum.

Glucocorticoids are used in all current treatment regimens for 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 7. In view of the established efficacy associated with combined immunosuppression, there is a move towards reducing glucocorticoid exposure.

The role of i.v. methylprednisolone pulses at the start of treatment has not been well-studied, but i.v. glucocorticoid is commonly given as up to 3 daily doses of 500 mg each (range 250–1000 mg/d). There is general agreement to start treatment with i.v. pulse methylprednisolone 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. In contrast, opinions vary on the use of i.v. methylprednisolone in patients with milder disease manifestations. As shown in Figure 7, "high-dose" glucocorticoid schemes in earlier clinical trials could start with no i.v. methylprednisolone but with high-dose oral prednisone, while glucocorticoid schemes adopted in more recent clinical trials often began with i.v. methylprednisolone pulses followed by oral prednisone at a relatively lower dose and more-rapid tapering. Also, presently it is unusual for the daily prednisone dose to exceed 60 mg.

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 tapering of oral glucocorticoid in recent clinical trials.[107] 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.[142] In children, the avoidance of excessive glucocorticoid exposure also has implications for growth, psychosocial issues, and drug adherence.[143] 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 S12[144–146]). 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 7. They serve to illustrate variations in exposure to glucocorticoids over time. The certainty of evidence supporting any of these regimens is low as they have only been compared in relatively small clinical trials[144–146] and observational studies.[147] The use of reduced-dose glucocorticoids may decrease the incidence of major infections and other adverse effects. Accumulating evidence shows that reducing glucocorticoid exposure in combined immunosuppressive regimens is feasible in the treatment of LN, with maintained efficacy while reducing the glucocorticoid-related toxicities.[146,148]

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

Cyclophosphamide may be given orally or intravenously, and in a high 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). Examples of dosing and duration for these regimens are given in Figure 6.

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

- *Efficacy:* Oral and high-dose i.v. cyclophosphamide regimens have been used in diverse ethnic populations and for all levels of disease severity, and show equivalent efficacy.[18,149–152] Low–dose cyclophosphamide (Euro-Lupus regimen) shows efficacy equivalent to that of standard-dose cyclophosphamide but was tested mainly in White patients.[17,99] Emerging data suggest low-dose cyclophosphamide is effective in Asians, Hispanics, and Black patients, but these studies did not make direct comparisons to high-dose i.v. cyclophosphamide (Supplementary Table S6[17,121–124,153]).
- *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 come to the healthcare facility for regular drug infusions but results in rapid increase in cumulative exposure.
- *Toxicity:* The toxicities of cyclophosphamide may be considered immediate (e.g., gastrointestinal, susceptibility to infection) or delayed (e.g., loss of fertility, future malignancies).
  - High-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 S13[13,154]). 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/m^2 for young to older pediatric patients, respectively; 300 mg/kg for adults).

In view of its toxicities, including the increased risk of malignancies, the exposure to cyclophosphamide should be minimized to the extent possible.

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

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 that of oral or i.v. cyclophosphamide for induction of complete and partial renal responses (Supplementary Table S7[13–15,102,121,125–128]). 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.[146]

Although use of 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.[155] 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 h/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.[156–160]

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.[12,139] 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.[140] 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%, $P = 0.24$).[12,139] 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 SCr level at presentation showed a comparable early response to glucocorticoids plus either cyclophosphamide or MMF.[161] 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,[16] although the difference was 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.

CNIs 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.[19,162,163] 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 that in controls treated with the NIH-cyclophosphamide regimen, with a higher complete renal response rate (46% vs. 26%) after 24 weeks of treatment.[19] Extended follow-up, however, showed comparable renal response rates in both groups during the second year of treatment.[106] 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.[162]

The evidence from the few RCTs that compared triple therapy to cyclophosphamide is judged as having low certainty because of study limitations and indirectness (Supplementary Table S8[19,103,104,121]). 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 that 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 CNIs.[163]

Voclosporin is an analog 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.[164] Voclosporin for the treatment of active biopsy-proven Class III, IV, and V LN was investigated in the AURA-LV trial,[107] a phase 2 RCT of 265 subjects and the AURORA 1 trial,[108,165] 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 i.v. 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 ≤0.5 mg/mg [50 mg/mmol], eGFR ≥60 ml/min per 1.73 m^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 (odds ratio [OR] 2.03, P <0.05).[107] Similarly, in AURORA, 41% of voclosporin-treated patients achieved RR at 52 weeks, compared to 23% of placebo-treated patients (OR 2.65, $P < 0.001$).[108,165] 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).[166] The incidences of 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 is not necessary in the studied patient population.[167] Note that there are no data on voclosporin given together with cyclophosphamide.

Results from the 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 ≤45 ml/min per 1.73 m^2, and these patients were excluded from the trials. Similarly, significant

impairment of kidney function is often an exclusion criterion in clinical trials of CNIs. The use of a CNI in patients with severe CKD requires careful individualized consideration of risk versus potential benefit, and should be done with caution and careful monitoring, and at reduced drug exposure.

The positive results of AURA-LV and AURORA coupled with those of 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 [>6.2 nmol/l]) 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%).[168] 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 the induction phase. The evidence for efficacy for this trial is considered to be of low-to-very low certainty (Supplementary Table S14[101,126,168–170]). Data from 10-year follow-up reported a higher incidence of kidney flares in patients treated with tacrolimus during the induction phase (53% vs. 34%), while long-term kidney function was similar between the 2 groups.[170] A more recent open-label clinical trial randomized 314 patients to tacrolimus (target trough level 4–10 ng/ml [5–12.4 nmol/l]) or i.v. cyclophosphamide and reported non-inferior 6-month responses between groups, with similar rates of adverse events (Supplementary Table S15[171–173]).[173]

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

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.[111] 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 low-dose cyclophosphamide regimen chosen by the site investigator. PERR was defined as a ratio of PCR of <0.7 g/g [70 mg/mmol], an eGFR that was no worse than 20% below baseline or at least 60 ml/min per 1.73 m^2, and no use of rescue therapy for treatment failure. At week 104, significantly more patients who received belimumab achieved a PERR compared to the number of patients who received placebo (43% vs. 32%; OR 1.60; $P = 0.03$; Supplementary Table S11[111]). Key secondary endpoints included complete renal response and the risk of kidney 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. In this context, extended follow-up data from open-label continuation studies in patients with SLE showed no new safety concerns when belimumab was used for 8–13 years.[174,175] 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.[176–178] An important observed effect of belimumab therapy in the BLISS-LN trial was the prevention of disease flares.[113] The follow-up for 2 years and an open-label follow-up for an 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.[111,112]

In *post hoc* subgroup analysis of this study, the efficacy benefit of belimumab appeared restricted to patients who received MMF versus cyclophosphamide, and to patients with proteinuria in the non-nephrotic range. Also, those who self-identified as Black race (63 of a total of 446 patients in the trial) appeared to have a lower treatment response rate compared with other racial groups, while the response rate with belimumab added was higher compared with placebo.[111,113]

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 high-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[13,179,180]). 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.[181,182] 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 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 S17[18,62,183–186]), and the anti-interleukin-6 antibody sirukumab (Supplementary Table S18[187]). However, 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 S19[188]).

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.[141,189–193] The negative outcomes contrast with reports of case series that suggested efficacy when patients with suboptimal response to standard therapy were treated with rituximab.[194–197] 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.[141,189] 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.[198]

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[141,153,189,191,195]).[198]

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.[192]

Anifrolumab is a human monoclonal antibody that binds to the type I interferon receptor unit 1 and has been recently approved by the U.S. FDA for treatment of nonrenal 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).

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,[11,17,19,199]

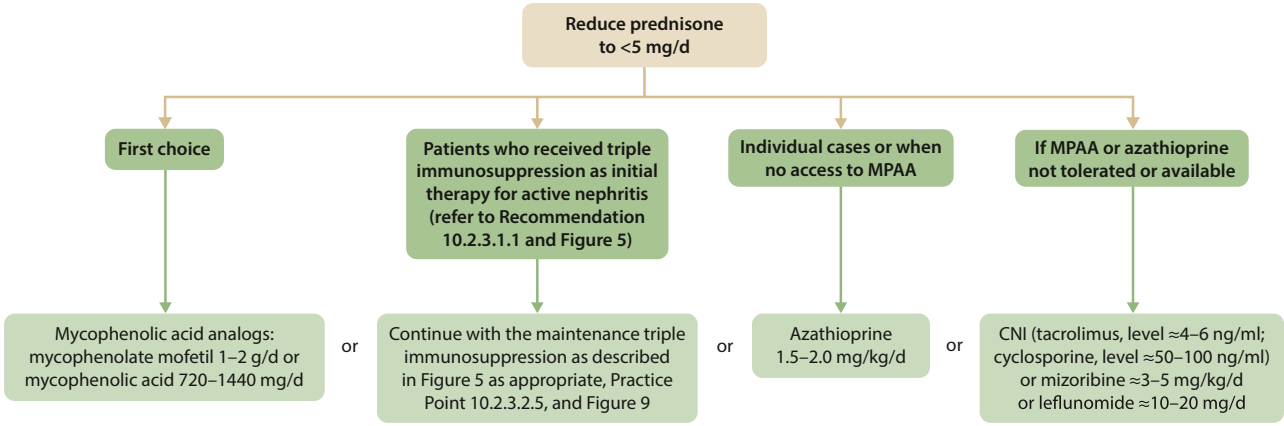

Figure 8 | Recommended options of maintenance therapy for Class III and Class IV lupus nephritis. The target ranges of calcineurin inhibitors (CNIs) have been based on the transplant literature. The Kidney Disease: Improving Global Outcomes (KDIGO) Work Group acknowledges that targets for glomerular 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 the serum creatinine level increases but does not plateau or increases to over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. MPAA, mycophenolic acid analogs.

and approximately 20% achieve complete histologic remission, defined as an activity index of zero on repeat kidney biopsy.[10] Also, LN relapses frequently, and relapses predispose patients 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.[119] This led to considerable lifetime cyclophosphamide exposure and toxicity.[200,201] A study reporting 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.[202] 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.[115,116] 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 S24[12,202–204]).[16,99] 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 ($P = 0.003$).[16] 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.[99] 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 a "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.[106] However, the follow-up duration of 18 months was

Maintenance immuno-suppressive regimens	Low-dose glucocorticoids AND					
	Mycophenolic acid analogs	Azathioprine	Belimumab and mycophenolic acid analogs or azathioprine	CNI and mycophenolic acid analogs	CNI (such as voclosporin, tacrolimus or cyclosporine)	Mizoribine
Comments	Preferred treatment based on high-certainty evidence; lower flare rate than azathioprine maintenance	Low medication cost; safe in pregnancy	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]	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]	Tacrolimus and cyclosporine safe in pregnancy; insufficient pregnancy data on voclosporin	Experience mostly in Japanese patients

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

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.

Relatively favorable results demonstrating sustained benefit have been reported for continued maintenance immunosuppression with triple immunosuppressive treatment regimens that included low-dose glucocorticoids and MPAA or azathioprine plus belimumab; low-dose glucocorticoids and MPAA plus voclosporin; or low-dose glucocorticoids and MPAA or azathioprine plus cyclosporine or tacrolimus (Figures 8 and 9).[108,110,113,205–207] Nevertheless, the optimal duration of such treatment remains unclear.

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.

Certainty of evidence. Three RCTs compared azathioprine with mycophenolate mofetil. There was moderate certainty of evidence that azathioprine probably increases renal relapse, risks for doubling of SCr, and leukopenia 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[12,202–204]).

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; thus, no conclusions were able to be drawn (Supplementary Table S25[119]).

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[202]). Thus, the findings of this review are inconclusive.

The ALMS trial compared azathioprine with MMF as maintenance therapy in patients with proliferative LN and showed an increased rate of a composite "treatment failure" endpoint and adverse effects (e.g., leukopenia) in patients who received azathioprine.[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 10.2.3.2.6[208–211]), and there is a lack of information regarding addition of B-cell–directed therapies to the maintenance phase.[212]

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, given the better efficacy of MPAA with its generally favorable tolerability profile, compared to azathioprine, 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 MPAAs are 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. Outside of medication expense, major resource implications arise 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.[213] 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 are 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 are 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 the U.S., while tacrolimus is classified under category C by the TGA and is not assigned a category by the FDA. Data from animal studies showed potential adverse effects that 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 are 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. In this regard, most preparations of cyclosporine also contain alcohol. Low-dose azathioprine is safe during pregnancy.

There are insufficient data on the safety of belimumab during pregnancy, and its use cannot be recommended at this time.[214]

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 as initial therapy and 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.[16,203] 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. 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,[15,118] and that long-term maintenance treatment with MPAA was associated with a low disease flare rate.[215] 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.[146,148] 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).[216] 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. It should be noted that the withdrawal of glucocorticoids in this study may have been too abrupt for patients who had been taking glucocorticoids for many years, in which case, the "flares" presented may in fact have been withdrawal symptoms. 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.[198]

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

The suggested dosages are largely based on data from the ALMS and MAINTAIN trials.[16,203] 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. The dose of MPAA may need to be reduced when kidney function is significantly impaired, as patients with CKD are more susceptible to the adverse effects of MPA. 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 patients who manifest or are at increased risk of drug toxicities. There are preliminary data associating disease flares with low MPA exposure, but the optimal drug level at different phases of clinical management remains to be determined.[217]

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 it is 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 consideration of 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 g/d for 2–3 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 toward higher renal relapses in the discontinuation group (Supplementary Table S27).[218]
- In Chinese patients who received MMF as initial therapy, discontinuation of MMF before 2 years was associated with an increased risk of disease flare.[15,118]
- 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 (6.2 μmol/l) remained in remission.[219]
- The ALMS maintenance phase data demonstrated 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.[220]
- Despite ≥36 months of immunosuppression and ≥12 months of sustained complete clinical renal response, 28%–50% of patients continued to show inflammatory histologic activity on repeat kidney biopsy.[221–223] 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.[222,223]
- 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 but are clinically only in partial remission due to residual proteinuria.[221–223] 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 the unknown 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 can 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 a 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 until 100 weeks from baseline with the primary endpoint assessed at week 104.[111] This was followed by an open-label extension study of 28 weeks that included 257 of the original 448 patients randomized in the BLISS-LN trial, during which patients originally randomized to receive placebo were changed to belimumab.[112] 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.[112,113]

In the phase 3 voclosporin trial in LN (AURORA 1), treatment was continued for 52 weeks and the primary endpoint was assessed at week 52.[141] 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).[110] 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.[106] 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 that of 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.[209,224] 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.[225]

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.[208,210,226–228] 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 cyclosporine can also be used safely during pregnancy (Figure 9).

The experience with mizoribine as maintenance therapy in LN is largely limited to Japanese patients.[211,229] 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).[230]

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 kidney 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[231]). There are no formal studies comparing leflunomide and MPAA; therefore, leflunomide is considered an alternative to MPAA in the above-mentioned circumstances exclusively. Leflunomide is contraindicated in pregnancy and should be discontinued for at least 2 years before patients try to conceive.

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. The management of Class V LN with no proliferation

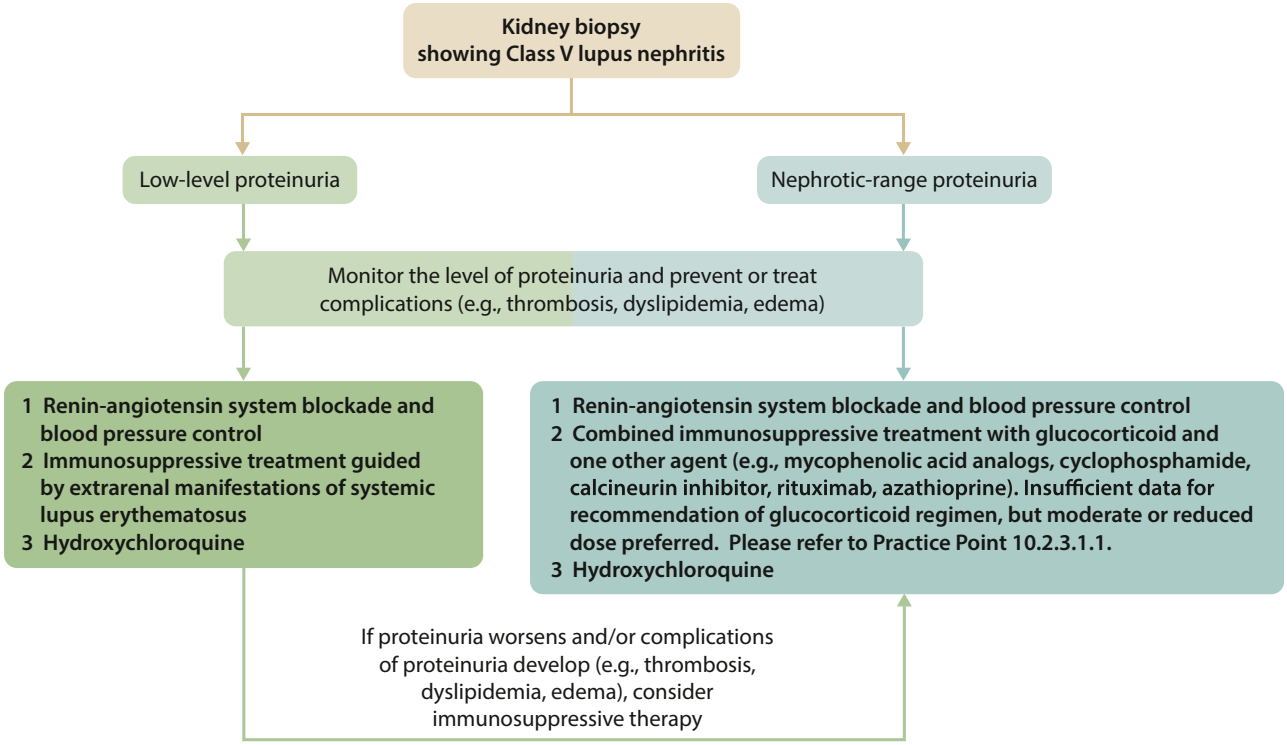

Figure 10 | Management of patients with pure Class V lupus nephritis.

in the kidney histology is guided by the severity of proteinuria. Long-term follow-up data show that 10%–30% of patients with Class V LN progress to kidney failure, and the risk of progressive CKD is associated with the severity of proteinuria. Unlike primary membranous nephropathy, heavy proteinuria in Class V LN does not usually spontaneously remit. Also, heavy proteinuria and NS increase the risk of infections and CV morbidity and predispose patients to thrombosis.[232–235]

A small RCT demonstrated that remission was significantly more likely with prednisone plus cyclophosphamide (60%) or prednisone plus cyclosporine (84%) than with 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).[149] Pooled data from 2 studies showed that prednisone plus either cyclophosphamide or MMF had similar efficacy in lowering proteinuria after 6 months of treatment.[236] Other studies with relatively small sample sizes reported the efficacy of glucocorticoids combined with azathioprine,[27,219] oral cyclophosphamide,[237] i.v. cyclophosphamide,[149,238] MMF,[26,27,168,238–240] CNIs,[149,168,227,241–243] and rituximab,[198,244] with response rates of 40%–60%. Triple immunosuppression with glucocorticoids, tacrolimus, and low-dose MPAA resulted in a higher complete remission rate in patients with Class V LN compared to that in controls treated with glucocorticoids and high-dose cyclophosphamide followed by azathioprine (33.1% vs. 7.8%).[19] Also, 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.[210] In the phase 3 voclosporin trial (AURORA; see Practice Point 10.2.3.1.4), 14% of the patients had pure Class V LN.[165] Adding voclosporin to background therapy was more effective than background immunosuppression alone in achieving renal response, and in 31 patients with Class V LN, the median time to reduce proteinuria to ≤0.5 mg/mg (50 mg/mmol) was 3.6 months in patients treated with voclosporin added to glucocorticoids and MMF, compared with 8.3 months in controls treated with placebo added to glucocorticoids and MMF (HR 1.93, $P = 0.167$).[245] In the BLISS-LN trial, 16% of patients had Class V LN (36 patients treated with belimumab, and 36 patients treated with placebo). Results from *post hoc* analysis suggested that belimumab might not be as effective in patients who presented with nephrotic-range proteinuria compared to those with less-severe proteinuria, although it might still reduce the incidence of adverse kidney outcomes. The overall increase in PERR and complete response rate (CRR) when belimumab was added to standard therapy was attributed to patients with a proliferative histologic component, while there was no observed treatment difference associated with belimumab in patients with Class V LN (PERR: OR: 0.65; 95% CI: 0.23–1.86; CRR: OR: 0.83; 95% CI: 0.27–2.62).[113] There is a lack of robust data in the management of Class V LN, especially in patients who present with NS. 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

Criteria	Definition
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
Primary efficacy renal response	• PCR ≤0.7 g/g (70 mg/mmol) • eGFR that was no worse than 20% below the pre-flare value or ≥60 ml/min per 1.73 m^2 • No use of rescue therapy for treatment failure
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • 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 | Definitions of response commonly used in clinical trials of lupus nephritis. *For children <18 years old, complete response is defined as proteinuria <0.5 g/1.73 m^2 per day or <300 mg/m^2 per day based on a 24-hour urine specimen. eGFR, estimated glomerular filtration rate; PCR, protein–creatinine ratio.

blood pressure control, MMF is a reasonable first choice for treating patients with Class V and nephrotic-range proteinuria. If ineffective, we advise cyclophosphamide for ≤6 months next to help 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. Decisions on whether to treat with immunosuppressive medications or CNI in patients with proteinuria that is non-nephrotic but above 1 g/24 h need to be individualized, taking into account the severity and progression of proteinuria and the risks and benefits of treatment. 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).

10.2.5 Response and relapse considerations

10.2.5.1 Assessing treatment response in LN

Practice Point 10.2.5.1.1: Definitions of response to therapy in LN used in clinical trials are provided in Figure 11.

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.[115,246–248] 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.[117,249–251] In this regard, the PERR at Week 104 was the primary endpoint in the BLISS-LN trial.[111]

Another caveat is the lack of consensus on the appropriate time for assessing response. 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.[12,14,15,150,227,252,253] The timeframes for response assessment as stated in the definitions in Figure 11 refer to the timepoints when these outcomes are assessed in clinical trials. These timeframes do not mean that one would need to wait for the specified time periods to lapse before making management decisions. Instead, patients should be assessed continuously to ensure that there is continuous improvement, and in patients not responding satisfactorily to current therapy, alternative treatments should be considered early.

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 ≥25% reduction of proteinuria after 8 weeks of treatment.[254]

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., Systemic Lupus Erythematosus Disease Activity Index [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.[221–223] A repeat kidney biopsy may, therefore, be useful in confirming renal response, especially before making important major treatment decisions such as discontinuation of immunosuppression.[10] Also, holistic management should include considerations of CKD progression and CV risk factor management, in addition to minimization of other long-term adverse outcomes.

10.2.5.2 Management of unsatisfactory response to treatment

Practice Point 10.2.5.2.1: An algorithmic approach to patients whose response to therapy is deemed unsatisfactory is provided in Figure 12.

Judging the response to therapy to be 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 minimizing 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 timeframe to see improvement was suggested based on *post hoc* analysis of data from the ALMS trial,[254] 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 overemphasized. The prevalence of nonadherence in patients with SLE could be >60%.[255–258] It is imperative therefore to check treatment adherence on a regular basis. Switching from oral immunosuppression to i.v. cyclophosphamide should be considered when nonadherence is suspected or known.

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 sizes.

The role of switching between therapeutic regimens has not been formally investigated. In a U.S. 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.[102] Another study reported efficacy of MMF in patients refractory to or who had relapsed after cyclophosphamide treatment.[259] 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%[190,215,260–271] and a meta-analysis of

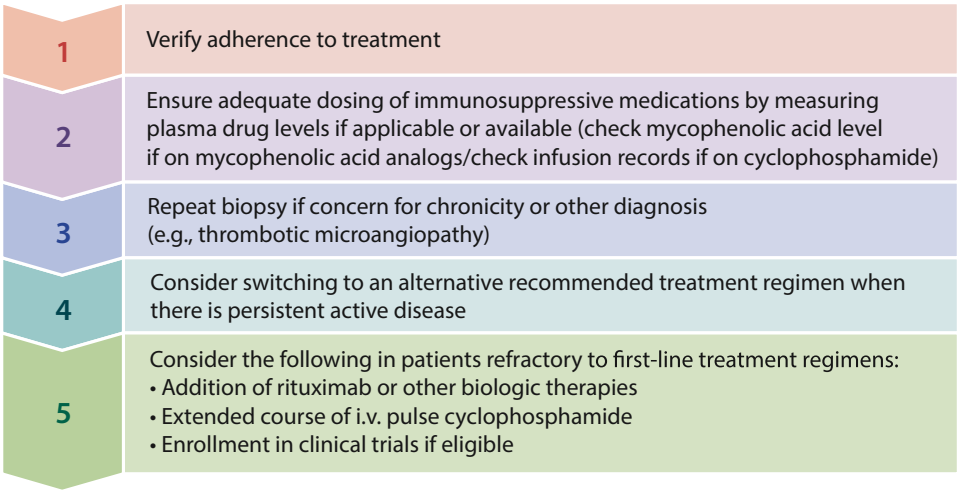

Figure 12 | Management of patients who show unsatisfactory response to initial therapy for active lupus nephritis. i.v., intravenous.

31 studies with 1112 patients that showed complete and partial response rates of 46% and 32%, respectively, after rituximab was added.[272] 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.[206,208,273–277] Other therapies under investigation may offer potential options for refractory LN, such as anti-CD19 chimeric antigen receptor T (CAR-T) cell therapy.[278]

10.2.5.3 Treatment of LN relapse

Relapses of LN are common, and LN flare is an important predictor of poor long-term kidney survival.[279–282] LN flare rates of 10%–50% have been reported, and relapses occur over time.[283] Failure to achieve complete remission increases the risk of subsequent relapse.[97,115,284] 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.[97] Similarly, an HR of 6.2 for relapse was reported in Chinese patients who did not achieve complete remission after initial therapy.[115]

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

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 to be applied in 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.[285] All LN clinical trials testing initial, induction therapies for LN include both types of patients. Although these considerations form the basis for Practice Point 10.2.5.3.1, there are several caveats in choosing an approach:

- 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/m^2.[286,287] 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.
- If patients relapse during pregnancy, treatment choices are more limited. These are discussed in Section 10.3.2.
- Patient preference and/or tolerance of the initial regimen should be considered. Also, patient adherence should be considered in the choice of treatment.
- 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 identify 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.[288]

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%.[289] 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 LN relapses) 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), none of the patients given prednisone had a severe flare, but 6 placebo patients did, and 3 of the flares were kidney-related.[290] 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.[217] 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 13[1].

TMA is a pathologic description of vascular endothelial injury secondary to various etiologies.[291] The causes of TMA

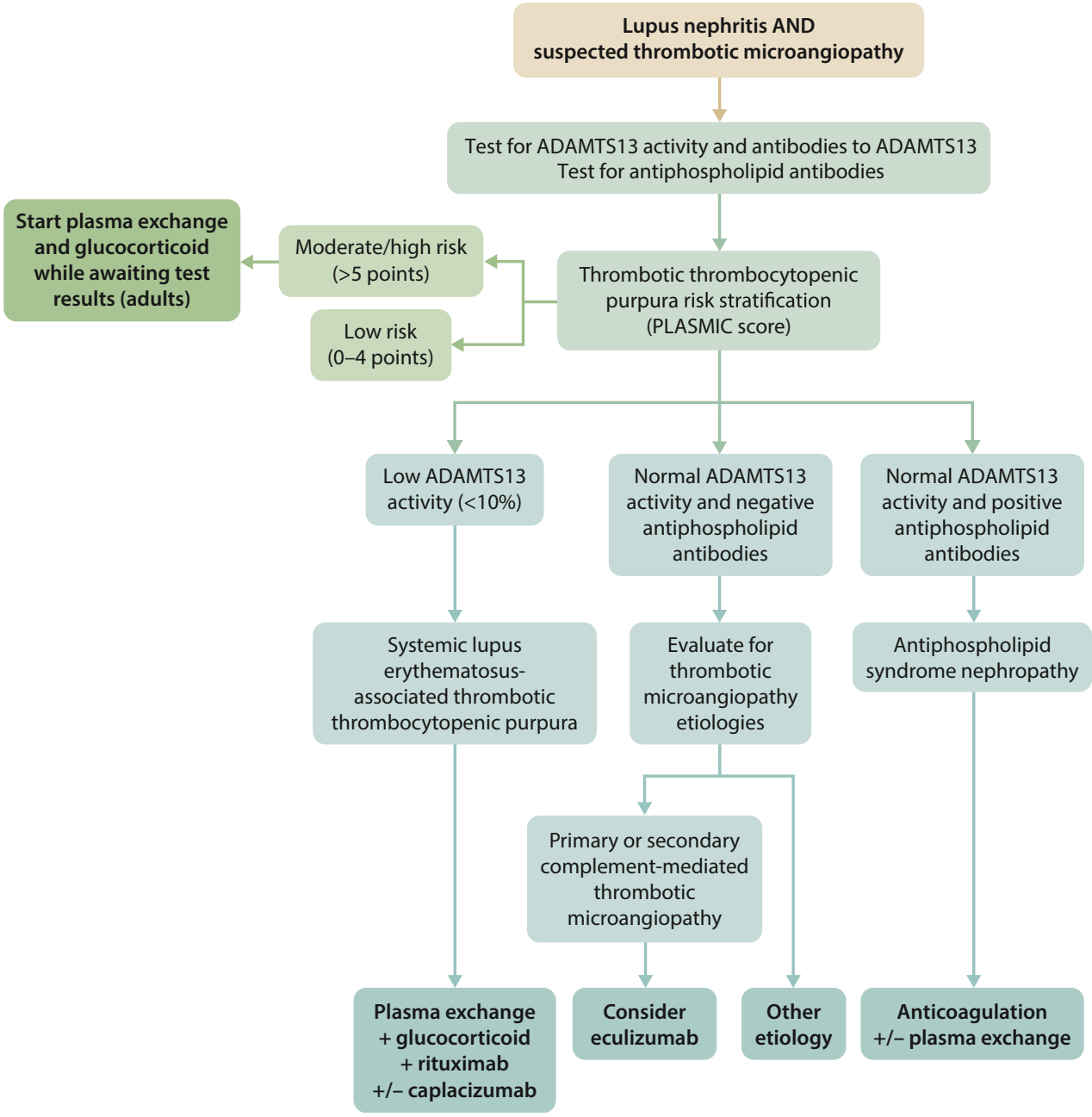

Figure 13 | Management of patients with lupus nephritis and thrombotic microangiopathy (TMA). Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol*. 2017;4:e157–e164.[1] ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PLASMIC, Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem-cell or solid-organ transplant, mean corpuscular volume (MCV), international normalized ratio (INR), Creatinine.

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.[292,293] 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 activity of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) 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 scoring through the PLASMIC (Platelet count, combined hemoLysis variable, absence of Active cancer, absence of Stem-cell or solid-organ transplant, MCV, INR, Creatinine),[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,[294] 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.[295]

TMA due to lupus-associated TTP. The diagnosis of TTP is mainly reserved for patients with TMA and low ADAMST13 activity (≤10%).[291,296] The treatment of confirmed TTP in LN is extrapolated from that of acquired TTP and includes plasma exchange,[297,298] high-dose glucocorticoids,[299,300] rituximab,[301–304] and/or caplacizumab (von Willebrand factor inhibitor; Figure 13).[305,306]

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 APS nephropathy.[307] 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% tested positive for lupus anticoagulant, and 13.4% had APS.[308] 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%). 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.[309,310]

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.[311] Plasma exchange is often used in catastrophic APS[312] and has been associated with improved patient survival in retrospective studies.[313] There are recent anecdotal reports on the potential efficacy of rituximab in catastrophic APS.[314,315] 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.[316–318]

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.[319,320] 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.[321–323] The limited data to date show a high response rate, with resolution of TMA in 68% of patients with secondary aHUS.[324] 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.[325] Efficacy of eculizumab treatment was also reported in 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.[326] 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.[327]

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.[317]

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.[300,328,329] As complement studies often take some time to be returned, 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 circulating complement regulators 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.[330–333] 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.[325]

10.3.2 Pregnancy in patients with lupus nephritis

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

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

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

Adverse pregnancy outcomes, such as preeclampsia, preterm birth, and fetal loss, are more frequent in patients with active LN.[334,335] Commonly used medications for LN induction and maintenance therapy, particularly cyclophosphamide and MMF formulations, are toxic to the fetus and 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.[336]

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.[43,48,337] 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.[338,339] 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.[334] 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 are emerging data on the use of belimumab in pregnancy,[214] 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 are 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.

Hydroxychloroquine, tacrolimus, low-dose azathioprine, and prednisone have limited transfer into breast milk and are considered safe with breastfeeding. MPAA are contraindicated when patients are breastfeeding.[340]

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.[341–343] 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.[344,345]

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. Recently reported long-term data from 92 patients with biopsy-proven LN occurring before the age of 18 years, presenting in the time period 2001–2020, showed survival rates without advanced CKD, kidney failure, or death of 94.2%, 92.7%, and 83.2% at 5, 10, and 20 years, respectively. Induction immunosuppression was done using glucocorticoid and MPAA (36%) or cyclophosphamide (34%), while MPAA were the maintenance immunosuppressive medication in 55%.[346] 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. Treatment decisions for hyperlipidemia are risk-stratified, and statins may be given to children aged 8 years or above. 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.

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.[347–349]

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,[350,351] and transplanted patients have lower mortality than patients with lupus who remain on dialysis.[352] As clinical outcomes are better in patients with shorter durations of dialysis,[353,354] 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,[355] 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.[356–358] One important consideration is that patients who have antiphospholipid antibodies may experience dialysis vascular access clotting or allograft thrombosis and may require prophylactic anticoagulation.[359–361]

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 from B-cell–directed therapies initiated during the maintenance phase?

Methods for guideline development

Aim

This is an update of the Lupus nephritis chapter of the KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases published in 2021.[362] 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 LN. 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).[363] This guideline has been developed and reported in accordance with the AGREE II reporting checklist.[364]

The processes undertaken for the development of the KDIGO 2024 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 certainty of the evidence for each outcome
- Finalizing guideline recommendations and supporting rationale
- Grading the strength of the recommendations, based on the certainty 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 2024 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 a 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.[362] The majority of clinical questions for this guideline were based upon RCTs to avoid bias by design. Clinical questions adhered to the population, intervention, comparator, outcomes, and study design (PICOD) format (a list of critical and important outcomes was compiled after voting by 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.[362] Details of the PICOD questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 2[121].

All evidence reviews were conducted in accordance with the Cochrane Handbook,[365] and guideline development adhered to the standards of GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).[366]

Literature searches and article selection. For the KDIGO 2024 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 and updated on April 25, 2023. These search updates included terms for both LN and antineutrophil cytoplasmic antibodies (ANCA) vasculitis (which underwent updating concurrently with the chapter on lupus nephritis).

Table 1 | Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality • Kidney failure • ≥50% loss of GFR • Infection • Glucocorticoid-related adverse events • Malignancy
Important outcomes	• Complete remission/relapse • Annual GFR loss (minimum 3 years follow-up)

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 2 | Clinical questions and systematic review topics in PICOD format

PICOD criteria	Lupus nephritis
Clinical question	**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?**
Population	Patients with biopsy-proven LN
Intervention	Antimalarial therapy
Comparator	No treatment, placebo, or standard of care
Outcomes	Outcomes listed in Table 1
Study design	2021 Guideline: RCTs and observational studies 2024 Guideline: RCTs published in peer-reviewed journals
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 S30, S32, S33
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
Cochrane systematic reviews	Tunnicliffe DJ, et al. Immunosuppressive treatment for proliferative lupus nephritis. Cochrane Database of Systematic Reviews. 2018:6;CD002922[121]
SoF tables	Supplementary Tables S5–S29, S31, and S34–S49

LN, lupus nephritis; MCD, minimal change disease; PICOD, population, intervention, comparator, outcomes, study design; RCT, randomized controlled trial; SoF, summary of findings.

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. For the 2024 update, a total of 1556 citations were screened (for both LN and ANCA vasculitis) (Figure 14). From these, we found 21 new eligible articles on LN that addressed 16 new RCTs, in 17 publications, and 4 new analyses of previously included RCTs.

Data extraction. For the KDIGO 2024 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[367]:

- 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.[365]

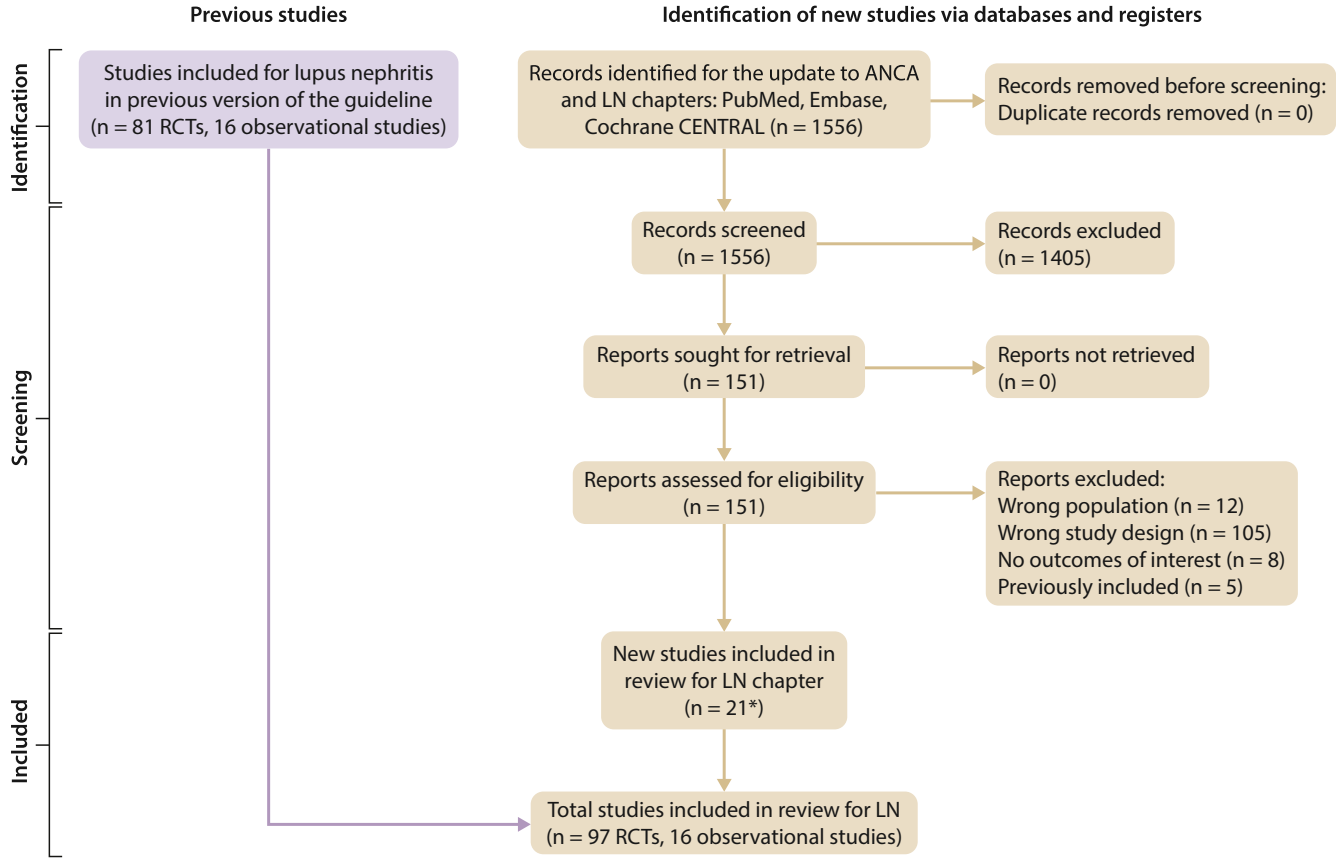

Figure 14| Search yield and study flow diagram. *16 RCTs in 17 records, and 4 new records from previously identified studies. ANCA, antineutrophil cytoplasmic antibody; LN, lupus nephritis; RCT, randomized controlled trial.

Assessment of heterogeneity. Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes, and of risk ratios, and by χ^2 tests. A P value of <0.1 was used to denote statistical heterogeneity, and an I^2 was calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.[365] We used conventions of interpretation as defined by Higgins *et al.*[368]

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).[365] 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).[365]

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 certainty of the evidence and the strength of a guideline recommendation. *GRADING the certainty of the evidence for each outcome across studies.* The overall certainty of the evidence related to each critical and important outcome was assessed using the GRADE approach,[366,369] which assesses the certainty of the evidence for each outcome. For outcomes that are based on data from RCTs, the initial grade for the certainty of the evidence is considered to be high. For observational studies, the initial certainty of the evidence is low. The certainty 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

Table 3 | Grading of certainty of the evidence

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

Table 4 | GRADE system for grading certainty of evidence

Study design	Starting grade for the certainty of evidence	Step 2—lower grade	Step 3—raise grade for observational evidence
RCTs	High	Study limitations: −1, serious −2, very serious	Strength of association +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: −1, serious −2, very serious	Evidence of a dose–response gradient
Observational studies	Low	Indirectness: −1, serious −2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: −1, serious −2, very serious	
		Publication bias: −1, serious −2, very serious	

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

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.[369] The final grade for the certainty 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 certainty of the evidence to be upgraded from a rating of low certainty, according to the specified criteria. For further details on the GRADE approach for rating certainty of the evidence, see Table 4.

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 certainty of evidence for each critical and important outcome is also provided in the SoF tables. For the 2024 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 2024 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 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 certainty of evidence in support of the recommendations.

Grading the strength of the recommendations. The strength of a recommendation is graded as Level 1, "we recommend" or Level 2, "we suggest" (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 certainty of the evidence, patient values and preferences, resource use and costs, and considerations for implementation (Table 6).

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 certainty of the evidence. The overall certainty 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 certainty 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

Table 5 | KDIGO nomenclature and description for grading recommendations

Grade	Implications		
	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	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.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

KDIGO, Kidney Disease: Improving Global Outcomes.

Table 6 | Determinants of the strength of recommendation

Factors	Comment
Balance of benefits and harms	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.
Certainty of evidence	The higher the certainty of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low certainty of the evidence will warrant a strong recommendation.
Values and preferences	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.
Resource use and costs	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

preferences of patients. Formal qualitative evidence synthesis on patient priorities and preferences was undertaken by the Cochrane ERT, 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,[370] 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 severity 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 (Level 1; or Level 2) and the certainty of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Certainty 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, nor 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.

Biographic and disclosure information

Jürgen Floege, MD (Work Group Co-Chair), is head of the Division of Nephrology and Immunology at the University of Aachen, Aachen, Germany since 1999.

Professor Floege is a former executive council member of International Society of Nephrology (ISN), European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), and Kidney Disease: Improving Global Outcomes (KDIGO). He is a Distinguished Fellow of the ERA-EDTA and recipient of the 2018 ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology, past President of the German Society of Nephrology, as well as an honorary member of the Japanese, Polish, Portuguese, Serbian, and Slovakian Societies of Nephrology. Together with Professors Richard Johnson, Marcello Tonelli, and John Feehally, he edits the best-selling textbook *Comprehensive Clinical Nephrology*. He is associate editor of *Kidney International* and a member of the editorial board of *Journal of the American Society of Nephrology* (*JASN*), *Journal of Nephrology*, and other journals. Until 2017, he served as associate editor of *Nephrology Dialysis Transplantation* (*NDT*).

His research interests encompass progression of kidney disease, in particular, kidney fibrosis, immune-mediated kidney disease, and IgA nephropathy, as well as chronic kidney disease-mineral and bone disorders (CKD-MBD) and cardiovascular disease in uremic patients.

His scientific work encompasses about 700 original papers, reviews, and editorials, and 40 book chapters.

JF reports receiving consultancy fees and/or speaker honoraria from AstraZeneca, Bayer, Calliditas, Chinook, GlaxoSmithKline, Novartis, Omeros, Otsuka, Stadapharm, and Travere; and serving on data safety monitoring boards for Novo Nordisk and Visterra.

Brad H. Rovin, MD, FACP, FASN (Work Group Co-Chair), is the Lee A. Hebert Professor of Nephrology at The Ohio State University Wexner Medical Center, Columbus, Ohio, USA. He is the Division Director of Nephrology and Medical Director of The Ohio State University Center for Clinical Research Management. Dr. Rovin conducts translational research on autoimmune glomerular diseases and applies these studies to clinical trial development and design for investigator-initiated and industry-sponsored trials of novel therapeutics.

BHR reports receiving consultancy fees from Alexion, AstraZeneca, Aurinia, Bristol Myers Squibb, Exagen, Genentech, GlaxoSmithKline, Kezar Life Sciences, Kyverna, Novartis, and Otsuka; and grant/research support from Biogen.*
**Monies paid to institution.*

Isabelle M. Ayoub, MD, is an Associate Professor of Medicine in the Division of Nephrology at The Ohio State University Wexner Medical Center. She works in a busy lupus, vasculitis, and glomerulonephritis clinic. She is the Director of the Nephrology Clinical Trials Unit at Ohio State University. Dr Ayoub's primary focus is in the area of glomerular diseases with a research interest in evaluating experimental therapeutics in glomerular diseases.

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

Tak Mao Chan, MBBS, MD, DSc, MRCP, FHKCP, FHKAM, FRCP, FASN, is the Yu Chiu-Kwong Chair of Medicine and Chief of Nephrology at the School of Clinical Medicine, The University of Hong Kong, China. He obtained his MBBS, MD, and DSc from the University of Hong Kong (HKU). He was promoted to Personal Chair Professor at HKU in 2005, and was appointed Yu Chair of Nephrology in 2008, then Yu Chiu-Kwong Chair of Medicine in 2011, and has been Chief of Nephrology since 2010. He has served as Associate Dean, member of the Senate, and member of the University Selection & Promotion Committee, and is now a member of the University Council at HKU. He was President of the Asian Pacific Society of Nephrology (APSN), Chairman of the Hospital Authority Coordinating Committee for Internal Medicine, and Council Member of the International Society of Nephrology. He has been President of The Hong Kong College of Physicians since 2022.

Dr. Chan's research focuses on lupus nephritis and viral hepatitis in patients with kidney diseases. His work contributed to the establishment of mycophenolate as standard-of-care induction and maintenance therapy for lupus nephritis and highlighted the role of different immunosuppressive treatments such as calcineurin inhibitors and mammalian

target of rapamycin (mTOR) inhibitors, and the importance of preventing nephritic flare and chronic kidney disease (CKD) in lupus nephritis management. His work also established the role of antiviral therapy for the prevention of hepatitis B flare in kidney transplant recipients. Translational studies from his laboratory investigate immunopathogenic mechanisms in kidney inflammation and fibrosis, and the role of resident kidney cells. Dr. Chan's publications have appeared in the *New England Journal of Medicine*, *Kidney International, Journal of the American Society of Nephrology*, *Arthritis Rheumatology*, *Nature Reviews Nephrology*, *Hepatology,* and *UpToDate*. He received the APSN Kenzo Oshima Award in 2014.

TMC reports receiving support for studies or manuscripts pertaining to this topic from Astellas and GlaxoSmithKline; and consultancy fees from AstraZeneca, GlaxoSmithKline, and Novartis.

Zhi-Hong Liu, MD, is a professor of medicine and academician at the Chinese Academy of Engineering, China. She is the Director of the National Clinical Research Center of Kidney Disease, Jinling Hospital, and Dean of the Zhejiang University School of Medicine. Dr. Liu is the past President of the Chinese Society of Nephrology. She was an executive committee member of the International Society of Nephrology and KDIGO. She is the Editor-in-Chief of *Kidney Diseases*, *Chinese Journal of Nephrology*, and *Dialysis & Transplantation*.

Dr. Liu has devoted herself to patient care, research, and medical education. Her primary interest is in the field of kidney disease, with a special interest in glomerulonephritis and diabetic nephropathy. She has edited 5 books on kidney disease, and is the chief scientist of the National Basic Research Program of China (973 Program) and was honored with the National Science and Technology Progress Award of China.

Z-HL declared no competing interests.

Juan Manuel Mejía-Vilet, MD, PhD, is a consultant nephrologist at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, a clinical researcher for the Mexican National Research System, and a professor of medicine for the National University of Mexico, Panamerican University, and the Monterrey Institute of Technology and Higher Education.

Dr. Mejia-Vilet received his medical degree from the University of San Luis Potosi. He was trained in internal medicine and nephrology at the National University of Mexico and completed an International Society of Nephrology Glomerular Diseases fellowship at The Ohio State University. He has a Master of Medical Science and a PhD degree from the National University of Mexico for his study of lupus nephritis pathophysiology and biomarker development.

His primary research area is centered on noninvasive biomarkers and prognosis of glomerular diseases, especially lupus nephritis and antineutrophil cytoplasmic antibody (ANCA) vasculitis. He currently follows a local lupus nephritis cohort comprising more than 700 subjects, and the local glomerular diseases registry, and actively participates in clinical trials in these areas.

JMMV reports receiving funding for educational presentations from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Roche; and serving on the advisory board for Kezar Life Sciences.

KDIGO Chairs

Michel Jadoul, MD, received his MD degree in 1983 at the Université Catholique de Louvain (UCLouvain), Brussels, Belgium. Dr. Jadoul trained in internal medicine and nephrology under the mentorship of Professor Charles van Ypersele de Strihou. He has served as chair of the Department of Nephrology of the Cliniques Universitaires Saint-Luc (2003-2023) and is currently a full clinical professor at UCLouvain. Dr. Jadoul's clinical activities focus on the follow-up of hemodialysis and chronic kidney disease (CKD) patients, and his main research interests include β2-microglobulin amyloidosis, hepatitis C, and other complications (e.g., falls, bone fractures, sudden death) in hemodialysis patients, as well as cardiovascular complications after kidney transplantation and various causes of kidney disease (e.g., drug-induced).

Dr. Jadoul has coauthored over 350 scientific papers, most of them published in major nephrology journals. He is currently serving as an associate editor of *Nephrology Dialysis Transplantation*, and he is also a country co-investigator for the Dialysis Outcomes and Practice Patterns Study (DOPPS) (2001–present). In 2008, he received the International Distinguished Medal from the U.S. National Kidney Foundation (NKF). He was previously a member of the European Renal Association Council (2013–2016). Presently, Dr. Jadoul is a Kidney Disease: Improving Global Outcomes (KDIGO) Co-Chair.

MJ reports receiving consultancy fees from Astellas, AstraZeneca*, Bayer*, Boehringer Ingelheim*, Cardiorenal*, CSL Vifor*, Fresenius Medical Care Asia Pacific*, GlaxoSmithKline*, Mundipharma*, and Vertex*; grants/research support from Amgen and AstraZeneca*; speaker honoraria from AstraZeneca*, Bayer*, and Boehringer Ingelheim*; providing*

expert testimony for Astellas and Stada-Eurogenerics*; receiving travel support from AstraZeneca*.*
**Monies paid to institution.*

Morgan E. Grams, MD, PhD, MHS, is the Co-Director of the New York University Division of Precision Medicine, a multidisciplinary research unit that aims to produce evidence to inform the delivery of high-quality, equitable patient care, responding rapidly to changes in health care guidelines, delivery, safety, and regulation. A practicing nephrologist, PhD-trained epidemiologist, and the Susan and Morris Mark Professor of Medicine and Population Health at New York University, Dr. Grams is Co-Principal Investigator of the Chronic Kidney Disease Prognosis Consortium (CKD-PC), a consortium of over 30 million participants, 100 cohorts, and 250 investigators from around the globe. In this role, Dr. Grams and the CKD-PC team focus on developing, testing, and implementing analytic strategies to answer clinically meaningful questions using as much of the world's data on kidney measures and outcomes as possible. She also leads efforts to integrate multimodal omics data as they relate to kidney disease. She was the winner of the Young Investigator Award in 2018 given by the American Society of Nephrology/American Heart Association Kidney Council, the top award for investigators under 45 years of age, and she is a member of the American Society of Clinical Investigation. She attended medical school at Columbia University and completed her nephrology fellowship at Johns Hopkins University.

MEG declared no competing interests.

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Marcello A. Tonelli, MD, SM, MSc, FRCPC, is a nephrologist, professor, and clinician–scientist at the University of Calgary, Calgary, Alberta, Canada.

Dr. Tonelli's research focuses on improving the care of people with chronic kidney disease and other noncommunicable diseases. He is chair emeritus of the Canadian Task Force on Preventive Health Care, a past President of the Canadian Society of Nephrology, and the President-Elect of the International Society of Nephrology. He is a member of the Governing Council for the Canadian Institutes of Health Research and the Director of the World Health Organization's Collaborating Centre for the Prevention and Control of Chronic Kidney Disease.

Dr. Tonelli has been named a Highly Cited Researcher each year since 2015 by Thomson Reuters Web of Science, corresponding to a rank in the top 0.1% by citations of all researchers worldwide.

MAT reports receiving payment for providing expert testimony from Gilead Sciences (not related to the guideline topic).

Evidence Review Team

Ethan M. Balk, MD, MPH, is Associate Director of the Center for Evidence Synthesis in Health, and Professor of Health Services, Policy and Practice at Brown University School of Public Health in Providence, RI, USA. He has been Project Director of the ERT and has collaborated on numerous Kidney Disease: Improving Global Outcomes (KDIGO) guidelines since 2008, and Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines since 2000. As project director for this guideline, he played a pivotal role in providing methodological expertise in the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence and the revisions of the final evidence report. Dr. Balk also provided methodological guidance and training of Work Group members regarding topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research interests are evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal.

EMB declared no competing interests.

Craig E. Gordon, MD, MS, is Associate Professor of Medicine at Tufts University Medical Center in Boston, MA, USA. Dr. Gordon graduated from New York University School of Medicine and received a master's degree in clinical care research from the Tufts University School of Graduate Biomedical Sciences. Dr. Gordon previously served as the assistant project director of the ERT for the 2020 KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation and associate director of the ERT, and assistant project director for the 2018 and the 2022 KDIGO Clinical Practice Guideline on HCV in CKD.

Dr. Gordon provided methodologic expertise to the Work Group during the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence for the guideline, as well as providing guidance to Work Group members in the areas of topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research and clinical interests are in the management of HCV in patients with CKD, polycystic kidney disease, and

thrombotic microangiopathies, as well as evidence-based medicine and systematic review related to other areas of nephrology.

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

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