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2024 American College of Rheumatology (ACR) Guideline for the Screening, Treatment, and Management of Lupus Nephritis

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Objective. The objective is to provide evidence-based and expert guidance for the screening, treatment, and management of lupus nephritis.

Methods. The Core Team developed clinical questions for screening, treatment, and management of lupus nephritis using the PICO format (population, intervention, comparator, and outcome). Systematic literature reviews were completed for each PICO question, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the quality of evidence and to formulate recommendations. The Voting Panel achieved a consensus ≥70% on the direction (for or against) and strength (strong or conditional) of each recommendation.

Results. We present 28 graded recommendations (7 strong, 21 conditional) and 13 ungraded, consensus-based good practice statements for the screening and management of lupus nephritis. Our recommendations focus on the unifying principle that lupus nephritis therapy is continuous and ongoing, rather than consisting of discrete induction/initial and maintenance/subsequent therapies. Therapy should include pulse glucocorticoids followed by oral glucocorticoid taper and two additional immunosuppressive agents for 3–5 years for those achieving complete renal response.

Conclusion. This guideline provides direction for clinicians regarding screening and treatment decisions for management of lupus nephritis. These recommendations should not be used to limit or deny access to therapies, as treatment decisions may vary due to the unique clinical situation and personal preferences of each individual patient.

SIGNIFICANCE/HIGHLIGHTS:

- Lupus nephritis (LN) therapy should be initiated as soon as possible after diagnosis.
- Conditionally recommended treatment for Class III/IV (with or without Class V) LN includes triple therapy with intravenous glucocorticoids followed by oral glucocorticoid (≤0.5 mg/kg/day prednisone, maximum dose 40 mg/day) taper and:
  a. Mycophenolic acid analog (MPAA) plus belimumab -or-
  b. MPAA plus a calcineurin inhibitor (CNI) -or-
  c. Euro-Lupus Nephritis Trial (ELNT) low-dose cyclophosphamide (CYC) plus belimumab (with substitution of MPAA after completion of CYC).
- Conditionally recommended therapy for pure Class V LN (≥1 g proteinuria) includes combination therapy with intravenous glucocorticoids followed by oral glucocorticoid (≤0.5 mg/kg/day prednisone, maximum dose 40 mg/day) taper and MPAA plus a CNI.
- A glucocorticoid taper goal of ≤5 mg prednisone daily by 6 months is conditionally recommended.
- The conditionally recommended duration of immunosuppressive therapy (beyond hydroxychloroquine) for people with LN who achieve a complete renal response (CRR) is 3-5 years.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease with a prevalence of 72/100,000 persons in the United States.[1] Lupus nephritis (LN) occurs in close to half of SLE patients and carries a mortality rate of up to 30% at 10 years; 10–22% of people with LN will develop end stage kidney disease (ESKD).[2,3] Among those with SLE, male sex, younger age, and African, Hispanic, American Indian/Alaska Native, and Asian ancestry increase the likelihood of LN and ESKD.[4–8] Socially disadvantaged individuals in medically underserved areas have worse kidney outcomes.[9–11]

The American College of Rheumatology (ACR) last published LN clinical practice guidelines in 2012.[12] Recommendations called for induction therapy with high-dose glucocorticoids plus mycophenolate mofetil (MMF) or cyclophosphamide (CYC) and endorsed mycophenolate for maintenance therapy. Since then, belimumab and voclosporin[13,14] have been approved by the US Food and Drug Administration (FDA) for LN treatment, prompting a conceptual shift from induction/initial and maintenance/subsequent therapy to one of combination, ongoing therapy targeting different arms of the immune system.[15–17] Evidence on the relative effectiveness and toxicity of systemic glucocorticoids has also evolved.[18]

Recommendations in this guideline follow certain guiding principles (Table 1) and assume the exclusion of alternative diagnoses. Most are conditional; they are based on systematic literature reviews, values, and preferences elicited from an LN Patient Panel, and the expert opinion of adult and pediatric rheumatologists and nephrologists and a rheumatology physician assistant. The recommendations are intended to promote optimal outcomes for the most encountered LN scenarios; they include therapies available in the United States as of 2024 and apply to LN in adults and children.[19–21] Additional pediatric-specific or older adult concerns are addressed in Good Practice Statements (GPS). We acknowledge that therapeutic decisions vary depending on clinical presentation and patient preferences, and are limited by access to specialists, procedures, and medications. When recommended medications are not available, this guideline should not preclude the use of available traditional therapies. Recommendations are not based on patient-reported race or ethnicity, as evidence

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Table 1. Guiding Principles*

The goals of LN treatment are to preserve kidney function, reduce morbidity and mortality associated with chronic kidney disease, and minimize medication-related toxicities.
Collaborative care from rheumatology and nephrology should be offered to people with LN whenever possible.
Shared decision-making between clinicians and patients is essential as it respects patient values and preferences, leading to better adherence and outcomes.
Healthcare disparities may impact outcomes in people with LN; equitable implementation of treatment recommendations aims to improve outcomes and alleviate health disparities.
Pediatric and geriatric good practice statements are included when applicable.

* LN, lupus nephritis.

for race- or ethnicity-specific treatment efficacy is limited and confounded by socioeconomic factors. We present 28 Grading of Recommendations Assessment, Development and Evaluation (GRADE)-generated recommendations (7 strong, 21 conditional) and 13 ungraded, consensus-based GPS.

METHODS

This guideline follows the ACR guideline development process and policy directing management of conflicts of interest and disclosures (https://rheumatology.org/clinical-practice-guidelines), which includes GRADE methodology.[22,23] (Supplementary Materials 1). The Core Leadership Team (LRS, RAM, AAskanase, BLB, MD, AD, LTH, BHR, MBFS) drafted clinical population, intervention, comparator, and outcomes (PICO) questions (Supplementary Materials 2). The Literature Review Team performed systematic literature reviews for the PICO questions, graded the quality of evidence (high, moderate, low, very low), and produced an evidence report (Supplementary Materials 3). The evidence was reviewed, recommendations were formulated by the Core Team and voted on by an expert Voting Panel. Additionally, a Patient Panel comprised of 15 people with LN (two of whom also served on the Voting Panel) informed the Voting Panel on patients' perspectives and preferences.

Consensus required ≥70% agreement on direction (for or against) and strength (strong or conditional) of each recommendation. A recommendation is categorized as *strong* if the panel is confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a *conditional* recommendation denotes uncertainty regarding the balance of benefits and harms, low quality of evidence, or that the recommendation is particularly sensitive to individual patient preferences and patient-provider discussion.

The strength of a recommendation determines its clinical implications and should be considered when interpreting and using it for patient care. For patients, a strong recommendation suggests that most people in their situation would want the recommended course of action and only a small proportion would not; for clinicians, it means most patients should receive the recommended course of action. With a conditional recommendation, the implication for patients is that most people in their situation would want the recommended course of action, but many would not; for clinicians, it means they should recognize that different choices will be appropriate for different patients and they must engage in shared decision-making with each patient to arrive at a management decision.

GPS are made when panel members are confident that there is unequivocal benefit or harm despite indirect or inadequate evidence. Some of the original 249 PICO-generated recommendations were combined into broader recommendations, some generated good practice statements, and some were relegated to a future research agenda.

Rosters of the Core Leadership Team, Literature Review Team, Voting Panel, and Patient Panel are included in Supplementary Materials 4. Search strategies and study selection details are provided in Supplementary Materials 5 and 6. Approval from Human Studies Committees was not required.

Scope

This guideline addresses screening and treatment for all people with LN regardless of age, race, ethnicity, and other individual patient variables. It is the first part of a broader ACR SLE guideline project; the second part will include a general approach to SLE therapy as well as organ-specific treatment recommendations.

RESULTS/RECOMMENDATIONS

Terminology, definitions, and abbreviations are summarized in Table 2; recommendations and good practice statements are listed in Table 3.

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Screening

In people with SLE without known kidney disease, we strongly recommend screening for proteinuria at least every 6–12 months, OR when experiencing extra-renal flares.

The Voting Panel stated that for recent onset, or recently active SLE, LN surveillance every 6 months is most appropriate, consistent with the 2023 ACR SLE quality measures.[24] Conversely, for those with longstanding and mild and inactive SLE, annual testing is adequate. This recommendation is strong, despite a lack of high-certainty evidence, because the risk of missing new onset LN requiring urgent treatment far outweighs the minimal risk of obtaining a urine sample.

Kidney biopsy

GPS: Prompt percutaneous kidney biopsy should be performed in people with SLE when LN is suspected (unless contraindicated or not feasible), as histopathologic biopsy

Table 2. Guideline terminology, definitions, and abbreviations*

Terminology	ACR LN Guideline Definitions[a]
Kidney biopsy	
Diagnostic	Biopsy performed to establish diagnosis and guide treatment
For cause	Biopsy performed in response to clinical indications or change in patient status
Per protocol	Biopsy performed according to a predetermined schedule or study protocol, regardless of clinical response
Therapy	
Initial / induction therapy	Prior terminology: Therapy prescribed immediately after diagnosis of new LN or flare of LN
Subsequent / maintenance therapy	Prior terminology: Therapy prescribed to patients on initial therapy for 6–12 months who have achieved at least a PRR
Lupus nephritis therapy	Preferred terminology: Ongoing therapy (ie, initial plus subsequent therapy) based on current recommendations for combination therapy that starts at diagnosis and continues throughout the treatment course TRIPLE therapy: GC (pulse intravenous: 250–1000 mg methylprednisolone daily × 1–3 days, followed by oral 0.5 mg/kg/day (maximum dose 40 mg/day) taper Plus: two immunosuppressive therapies, usually a) MPAA plus belimumab OR b) MPAA plus CNI OR c) ELNT low-dose CYC plus belimumab (MPAA substituted for CYC after CYC course is completed). DUAL therapy: GC plus one immunosuppressive therapy, usually MPAA or ELNT low-dose CYC
Renal response	
Complete renal response (CRR)	Within 6–12 months of starting therapy (may take >12 months): • Reduction in proteinuria <0.5 g/g (50 mg/mmol) (24-hour collection or urine protein/creatinine ratio); AND • Stabilization or improvement in kidney function (+ 20% baseline i.e. at least 80% of baseline)[b]
Partial renal response (PRR)	Within 6–12 months of starting therapy: • Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) (24-hour collection or urine protein/creatinine ratio); AND • Stabilization of kidney function (+ 20% baseline i.e., at least 80% baseline)[b]
Inadequate renal response/ Nonresponse	Lack of achieving at least a PRR despite adherence to appropriate treatment for active LN of any class by 6–12 months
Refractory disease	Persistently active disease and absence of at least a PRR to at least two different appropriate 6-month courses of therapy for active LN of any class
Proteinuria	Protein as measured by 24-hour collection (g/24hr) or random urine protein-creatinine ratio (g/g)
Glomerular hematuria	Urine sediment positive for acanthocytes, ≥5%, RBC casts
Decreased kidney function	Abnormal eGFR below expected level for age and clinical history, or decreasing eGFR with no attribution other than SLE[c]

* ACR, American College of Rheumatology; CNI, calcineurin inhibitor therapy; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ELNT, Euro-Lupus Nephritis Trial; GC, glucocorticoid; LN, lupus nephritis; MPAA, mycophenolic acid analogs; RBC, red blood cell; SLE, systemic lupus erythematosus.

[a] Terminology and definitions vary across specialties, guidelines, and clinical trials. Those listed here reflect the consensus of the Voting Panel as being both reasonable and relevant; however, no systematic analyses were performed, and others may prefer alternative definitions.

[b] Some experts and clinical trials have included a requirement for low dose of prednisone (eg, ≤5 mg/d equivalent) in addition to proteinuria and renal function requirements for CRR and PRR definitions; however, many do not. This was extensively discussed when definitions were created. Although GC dose is a part of validated SLE remission criteria, and while we recommend a goal of ≤5 mg/d prednisone equivalent by 6 months of therapy in this guideline, we did not consider this to be an appropriate mandatory criterion for the renal response definitions.

[c] Variably defined across studies – both irreversible damage and active disease impact kidney function and proteinuria and may require kidney biopsy to distinguish.

Table 3. Recommendations and good practice statements*

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICOs addressed
SCREENING:			
In people with SLE without known kidney disease, we strongly recommend screening for proteinuria at least every 6–12 months, OR when experiencing extra-renal flares.	Strong	Indirect evidence; Very low	P16(a) (revision)
KIDNEY BIOPSY:			
GPS: Prompt kidney biopsy should be performed in people with SLE when LN is suspected (unless contraindicated or not feasible) as histopathologic biopsy features will confirm the diagnosis, rule out mimicking diseases, and impact therapy decisions.			
In people with SLE who have proteinuria >0.5 g/g and/or impaired kidney function not otherwise explained, we conditionally recommend performing a percutaneous kidney biopsy.	Conditional	Low-Very low	P1(a-e) P3(e-h)
For people with treated LN in remission who present with suspected LN flare (increased proteinuria, hematuria, and/or worsening kidney function), OR for people with ≥6 months of appropriate treatment and ongoing or worsening proteinuria, hematuria, and/or decreased kidney function, we conditionally recommend repeat percutaneous kidney biopsy.	Conditional	Low-Very low	P2(a-e) P4(a-c)
TREATMENT OF ACTIVE LN (CLASS III/IV OR CLASS V)			
GPS: Prompt glucocorticoid treatment should be administered for suspected LN to suppress acute inflammation while awaiting a kidney biopsy and the histopathology results.			
GPS: Dosage of LN medications should be adjusted in people with decreased GFR at initiation of therapy and periodically.			
GPS: Adjunctive treatment with systemic anticoagulation for people with LN and significant risk factors for thrombosis (eg, low serum albumin in context of severe proteinuria) should be discussed with nephrology.			
IN PEOPLE WITH ACTIVE, NEW ONSET OR FLARE OF CLASS III/IV OR CLASS V LN:			
...If not already on HCQ treatment, we strongly recommend initiation and continuation of HCQ to manage and prevent lupus clinical manifestations, unless contraindicated.	Strong	Low-Very low	P15(a)
...**With any elevation in level of proteinuria, including <0.5g/g, we conditionally recommend the addition of RAAS-I therapy**.	Conditional	Low-Very low	P7(d) P9(a)
...We conditionally recommend pulse intravenous glucocorticoids followed by oral prednisone (≤0.5 mg/kg/d, max of 40 mg/d) with taper to a target dose of ≤5mg/day by 6 months.	Conditional	Moderate-low	P7(a-c) P8(a,b) P9 (a-c)
... Who have achieved and sustained a complete response after treatment with any (triple or dual) immunosuppressive therapy, we conditionally recommend a total duration of therapy of at least 3–5 years.	Conditional	Low	P8(o,p) P10(l,m)
IN PEOPLE WITH ACTIVE, NEW ONSET, OR FLARE OF CLASS III/IV (WITH OR WITHOUT CONCOMITANT CLASS V LN):			
... We conditionally recommend therapy with a triple immunosuppressive regimen consisting of pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus:	Conditional	Moderate-Low	P7 (j,k,n-q) P8 (f-h,k-m)
a) MPAA plus belimumab -or-			
b) MPAA plus CNI -or-			
c) Euro-Lupus Nephritis Trial (ELNT) low-dose CYC plus belimumab (MPAA substituted for CYC after CYC course is complete).			
... We conditionally recommend an MPAA-based regimen over a CYC-based regimen.	Conditional	Low-Very low	P7(g,h)
... With proteinuria ≥3g/g, we conditionally recommend a triple immunosuppressive regimen containing pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus MPAA plus CNI over a regimen containing belimumab.	Conditional	Low	P7 (l,p)

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICOs addressed
… With extra-renal manifestations, we conditionally recommend a triple immunosuppressive therapy that contains belimumab over a regimen containing a CNI.	Conditional	Low	P7(p2) (revision)
… We conditionally recommend a target MMF dose of 2–3g/d (or equivalent).	Conditional	Very low	P7(l)
… Receiving a CYC-based regimen, we conditionally recommend the ELNT low-dose CYC regimen over a high-dose monthly pulse IV regimen;	Conditional	Very low	P7(e)
We also strongly recommend the ELNT-low dose CYC regimen over a daily oral CYC regimen.	Strong	Very low	P7(f)
… Who have undergone triple immunosuppressive therapy and achieved a complete renal response, we conditionally recommend continuing the same immunosuppressive regime.	Conditional	Moderate-Low	P8.3 (revision) P8 (f-h,k-m)
…Who have undergone triple immunosuppressive therapy and achieved a partial renal response, we conditionally recommend individualizing therapy depending on clinical factors that include the trajectory of response.	Conditional	None	P8.4 (revision)
… Who have undergone dual immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a complete renal response, we conditionally recommend continuing therapy with MPAA over AZA.	Conditional	Low	P8.1 (revision) P8(d,e,j)
… who have undergone dual immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a partial renal response, we conditionally recommend escalating therapy to a triple immunosuppressive regimen.	Conditional	None	P8.2 (revision) P8 (v-x, aa-cc)
IN PEOPLE WITH ACTIVE, NEW ONSET, OR FLARE OF (PURE) CLASS V LN:			
…With proteinuria ≥1 g/g we conditionally recommend treatment with a triple immunosuppressive regimen consisting of pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily x 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, and MPAA plus CNI (over MPAA plus belimumab, or CYC plus belimumab).	Conditional	Indirect: Very low	P9(p)
…**with proteinuria <1 g/g, we conditionally recommend treatment with glucocorticoids and/or immunosuppressant therapy (MPAA, AZA, or CNI) over no glucocorticoid or other immunosuppression**.	Conditional	None	P9(b)
NON-RESPONSIVE OR REFRACTORY LN:			
GPS: Medication dose and patient adherence should be assessed as an important first step in evaluating inadequate response or refractory LN, as insufficient treatment is an important cause of non-response.			
In people with any LN class with nonresponse (i.e., have not achieved at least a partial renal response by 6–12 months) we conditionally recommend escalation of treatment:	Conditional	Very low-None	P11.1, P11.2 (revision)
· **For initial dual therapy, escalate to triple therapy (pulse intravenous glucocorticoids, 250–1000 mg methylprednisolone daily for 1–3 days, followed by oral glucocorticoid ≤0.5 mg/kg/day, maximum dose 40 mg/day taper, plus either MPAA plus belimumab, MPAA plus CNI, or ELNT CYC plus belimumab)**.			
· **For initial triple therapy, change to an alternative triple therapy or consider addition of an anti-CD20 agent as a second immunosuppressive**.			
In people with any LN class with refractory disease (i.e., failed two standard therapy courses), we conditionally recommend treatment escalation to a more intensive regimen, including addition of anti-CD20 agents, combination therapy with three non-glucocorticoid immunosuppressives (i.e., MPAA, belimumab and CNI), or referral for investigational therapy.	Conditional	Very low- None	P12.1, P12.2 (revision)
OTHER LUPUS KIDNEY DISEASE:			
GPS: Alternative etiologies of kidney dysfunction in people with SLE should be carefully excluded, including non-inflammatory etiologies such as hypertensive, diabetic, and medication-induced nephropathy.			

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICOs addressed
ADJUNCTIVE / NON-IMMUNOLOGIC TREATMENT:			
*GPS: Adjunctive and non-immunologic therapies and practices should be initiated in addition to appropriate immunosuppressive therapy to improve overall kidney health (*Table 4*).*			
GPS: In children with childhood-onset SLE (cSLE) and LN, glucocorticoid regimens should be reduced to pediatric-appropriate doses for children, as reduction of cumulative glucocorticoid dosing is critically important given the early age of onset of cSLE onset and attendant comorbidities.			
GPS: In children with cSLE and LN, clinicians should monitor for delayed pubertal onset and decreased growth velocity that can result from disease activity and glucocorticoid treatment and consider referral to pediatric endocrinology if indicated.			
GPS: For children with cSLE, a structured, intentional transition from pediatric to adult rheumatology care is indicated to avoid poor outcomes during this vulnerable period.			
GPS: For older people with LN, medication number, type, and dosage should be regularly assessed, given the risks of polypharmacy and age-related decline in GFR in this population.			
MONITORING LN ACTIVITY:			
In people with SLE and LN who have not achieved CRR, we strongly recommend quantifying proteinuria at least every 3 months.	Strong	Indirect evidence; Very low	P16(b,c) (revision)
In people with SLE with known nephritis in sustained clinical renal remission, we strongly recommend quantifying proteinuria every 3–6 months.	Strong	Indirect evidence; Very low	P16(d) (revision)
GPS: In people with LN, serum complement and anti-dsDNA antibody should be measured at every clinic visit (but not more frequently than monthly).			
RENAL REPLACEMENT THERAPIES:			
GPS: Decisions for initiation and type of dialysis and timing for kidney transplant require close collaboration with nephrology.			
In people with LN and ESKD, we strongly recommend kidney transplantation over dialysis.	Strong	High	P18(a)
In people with LN who have progressive loss of kidney function and are nearing ESKD (defined as an eGFR of 15 ml/min/1.73m^2), we conditionally recommend preemptive kidney transplant over dialysis/no preemptive kidney transplant.	Conditional	Very low	P22(a)
In people with LN and ESKD, we conditionally recommend proceeding with kidney transplantation without requiring complete clinical or serologic remission, provided there is no other major organ involvement.	Conditional	Very low	P23(a,b)
In people with LN on current dialysis or after kidney transplantation, we strongly recommend regular follow up with rheumatology.	Strong	Very low	P20(a,b)

* Anti-CD20 therapy: rituximab or obinutuzumab. AZA, azathioprine; CNI, calcineurin inhibitor therapies (cyclosporine, tacrolimus, voclosporin); CRR, complete renal response; CYC, cyclophosphamide; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate (various definitions are used in clinical studies; calculations of eGFR from creatinine in recent research do not include coefficients for race; however, earlier literature does); ESKD, end stage kidney disease; GFR, glomerular filtration rate; GPS, Good Practice Statements; HCQ, hydroxychloroquine; LN, lupus nephritis; MMF, mycophenolate mofetil; MPAA, mycophenolic acid analogs (including mycophenolate mofetil, or MMF, and mycophenolic acid, or MPA); PICO, population, intervention, comparator, outcome; RAAS-I, renin-angiotensin-aldosterone system inhibitors (including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists); SLE, systemic lupus erythematosus.

features will confirm the diagnosis, rule out mimicking diseases, and impact therapy decisions.

Biopsy should be read by a nephropathologist using the International Society of Nephrology (ISN) and Renal Pathology Society (RPS) classification[25] and include LN class and activity/chronicity indices. Risk of major bleeding with kidney biopsy, ie, requiring a blood transfusion or embolization procedure, is very low (~1–2%).[26–31] For people with SLE, risk may be higher (up to 3%) in specific subgroups including those with thrombocytopenia, decreased kidney function, and antiphospholipid syndrome.[26,32–35] Patient representatives shared concerns about the invasive nature of biopsy and emphasized the importance of physicians discussing the procedure's benefits and risks.

While we recommend prompt kidney biopsy with treatment based on histology, biopsy may not always be possible. In the absence of a kidney biopsy, those with nephritic features (eg, hematuria, hypertension, impaired kidney function) are usually best treated according to Class III/IV recommendations, and those with nephrotic features (eg, proteinuria, ≥3.5 g/g, hypoalbuminemia) according to Class V recommendations.

In people with SLE who have proteinuria >0.5 g/g and/or impaired kidney function not otherwise explained, we conditionally recommend performing a percutaneous kidney biopsy.

Kidney biopsy has value in people with SLE with isolated impaired kidney function that is not otherwise explained because histologic disease activity can occur without proteinuria.[36–39]

For people with treated LN previously in remission who later present with suspected LN flare (increased proteinuria, hematuria, and/or worsening kidney function), OR for people with ≥6 months of appropriate treatment and ongoing or worsening proteinuria, hematuria, and/or decreased kidney function, we conditionally recommend repeat percutaneous kidney biopsy.

Clinical judgment and patient preference are essential in deciding when to repeat kidney biopsy. With appropriate medication dosing and adherence, worsening kidney function or proteinuria should prompt consideration of repeat biopsy. Change in kidney histology is found in 40–50% of repeat biopsies.[40–42] While repeat biopsy for isolated significant/increasing hematuria can be considered when other etiologies are excluded, the value of biopsy in the setting of chronic low-level hematuria is uncertain. The Voting Panel did not issue a recommendation on per protocol (ie, scheduled) repeat kidney biopsies but considered this an important research item.

Treatment of LN:

GPS: Prompt glucocorticoid treatment should be administered for suspected LN to suppress acute inflammation while awaiting a kidney biopsy and the histopathology results.

GPS: Dosage of LN medications should be adjusted in people with decreased glomerular filtration rate (GFR) at the initiation of therapy and periodically as indicated during the disease course (Supplementary Materials 7).

GPS: Adjunctive treatment with systemic anticoagulation for people with LN and significant risk factors for thrombosis (e.g., low serum albumin in the context of severe proteinuria) should be discussed with nephrology.

Nephrology guidelines recommend treating patients with a serum albumin concentration below 2.0–2.5 g/dl in the setting of nephrotic range proteinuria with full-dose anticoagulation to prevent clotting unless the risk of bleeding is high.[43]

Class III/IV or Class V LN:

In people with LN who are not already on hydroxychloroquine (HCQ), we strongly recommend initiation and continuation of HCQ to manage and prevent extra-renal manifestations, unless contraindicated.

This is a strong recommendation based on low certainty evidence due to the well-established role for HCQ in overall SLE management. HCQ reduces risk of mortality in people with SLE, including those with lupus nephritis.[44–46] Dose adjustment for low GFR should be considered because kidney disease is a risk factor for retinal toxicity[46] (Supplement Materials 7).

In people with active, new onset or flare of LN with any elevation in proteinuria, including <0.5 g/g, we conditionally recommend the addition of renin-angiotensin-aldosterone system inhibitor (RAAS-I) therapy.

This recommendation applies to any level of persistent proteinuria above the normal range and is based on studies showing the kidney protective effects of RAAS-I in proteinuric LN and advanced chronic kidney disease (CKD).[47] Additionally, a pediatric study demonstrated that addition of RAAS-I led to earlier glucocorticoid discontinuation.[48] Use may be limited by blood pressure or estimated glomerular filtration rate (eGFR).

In people with active, new onset or flare of LN, we conditionally recommend pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) with taper to a target dose of ≤5 mg/day by 6 months.

A recent systematic review and meta-analysis determined that pulse glucocorticoids followed by oral glucocorticoids (up to 40 mg/day) maximized complete renal response while minimizing toxicities.[18,49–51] A range of pulse therapy dosing is presented to accommodate individualized treatment approaches.[52] Lower doses have been utilized in some recent treatment trials,[14] and patients emphasized their preference for minimizing glucocorticoid dose. The tapering regimen in clinical practice should be individualized and based on monitoring of both renal and extra-renal disease activity. Data informing the optimal dosing of glucocorticoids for pure Class V LN are limited.

In people with new onset or flare of LN who have achieved and sustained a complete renal response after treatment with any (triple or dual) immunosuppressive therapy, we conditionally recommend a total duration of immunosuppressive therapy of at least 3–5 years.

The advent of triple therapies blurred the distinction between induction therapy and maintenance therapy. Traditionally, patients were initially treated with one drug plus glucocorticoid followed by a "less toxic" drug for maintenance. Induction implied remission was achieved; however, in the short exposure to induction therapy (usually 3–6 months), most patients did not achieve remission. Maintenance implied maintenance of remission; but for most patients, maintenance served the initial purpose of consolidation.[53]

Current regimens aim to provide initial glucocorticoid and immunosuppressive therapies to rapidly reduce disease activity, with continuation of immunosuppressive therapies until disease is inactive, which often takes at least 12 months. Typically, some immunosuppressive therapy should be continued for at least

3–5 years of total treatment before considering withdrawal.[54,55] Support for a relatively long exposure to immunosuppression comes from repeat biopsy studies showing persistence of immunologic activity and immune complexes for several years after starting therapy; risk of LN flare is increased with withdrawal of immunosuppression while histologic activity remains.[56]

Over time, immunosuppressive therapy dosage may be tapered in stable patients as determined by renal and extra-renal disease activity and medication tolerability. No evidence provides robust guidance regarding optimal tapering practice; these decisions are currently made based on clinical expertise and patient preference. Risk of nephrotoxicity may impact decisions regarding the total duration of therapy with CNIs. HCQ should be continued indefinitely if there are no contraindications.

Class III/IV LN (with or without Class V LN):

Class III/IV LN lesions, characterized by endocapillary hypercellularity, are highly inflammatory and destructive. When occurring concomitantly with Class V, the presence of Class III/IV lesions drives therapy choice. Until complete renal response (CRR) is achieved, patients should be closely monitored and have therapies adjusted accordingly based on individual risk factors including blood pressure, proteinuria, and kidney function (Figure 1).

In people with active, new onset or flare of Class III/IV (±V) LN, we conditionally recommend therapy with a triple immunosuppressive regimen consisting of pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper plus:

a. **MPAA plus belimumab -or-**
b. **MPAA plus CNI -or-**
c. **Euro-Lupus Nephritis Trial (ELNT) low-dose CYC[53] plus belimumab (MPAA substituted for CYC after CYC course complete)**.

Recent randomized controlled trials (RCTs) suggesting overall improved outcomes with triple versus dual therapies guided discussion and voting for this recommendation.[13,14] While the trials were randomized and controlled, the certainty of evidence was assessed as low-moderate. The recommendation for triple therapy is conditional, ie, sensitive to individual patient preferences and patient-clinician discussion. A sensitivity analysis excluding Voting Panel members who had relevant conflicts of interest for this recommendation (5 of 21 members) resulted in no change in direction or strength.

Numerous factors will impact a decision regarding type of triple LN therapy. With eGFR ≤45, blood pressure >165/105, or significant chronicity on kidney biopsy, a belimumab regimen is preferred over a CNI regimen because of potential CNI-associated nephrotoxicity and hypertension

Randomized controlled trials demonstrated similar rates of response in people treated with MPAA and CYC-based regimens, however, the Voting Panel favored MPAA because of the better toxicity profile including lower risk of malignancy and lack of impact on fertility.[57] A CYC-based regimen might be favored in certain circumstances, however, including patient preference, medication non-adherence or intolerance, or the presence of rapidly progressive glomerulonephritis with numerous crescents and/or fibrinoid necrosis on biopsy and declining kidney function.

Data in support of ELNT low-dose CYC plus belimumab is more limited because only 26% of Belimumab International Study in Lupus Nephritis (BLISS-LN) trial participants were treated with background ELNT CYC.[58] Subgroup analysis of participants on background ELNT CYC showed a numerically higher but not statistically significant rate of renal response with addition of belimumab versus placebo. In a post-hoc analysis, addition of belimumab to ELNT CYC resulted in fewer LN flares and a reduced rate of eGFR decline compared to placebo[59]; for this reason, this combination was included as a recommended triple therapy.

The combination of ELNT CYC plus CNI has not been studied in RCTs; for this reason, it is not recommended here as triple therapy. However, this combination may be considered despite the lack of supporting data, especially if other therapy options are unavailable, ineffective, or not tolerated. Patient Panel members repeatedly emphasized the challenges of high pill burden, and preference for the route of medication administration (eg, parenteral or oral) may influence the choice of therapy.

In people with active, new onset or flare of Class III/IV (±V) LN with proteinuria ≥3 g/g, we conditionally recommend a triple immunosuppressive regimen containing pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus MPAA plus CNI over a regimen containing belimumab.

This recommendation was based on observed rapid reduction of proteinuria with CNIs[14] and the limited efficacy with belimumab in people with baseline proteinuria ≥3 g/g.[59]

In people with active, new onset or flare of Class III/IV (±V) LN with moderate to severe extra-renal manifestations, we conditionally recommend a triple immunosuppressive therapy that contains belimumab over a regimen containing a CNI.

Belimumab is associated with reduction in disease activity and severe flares in nonrenal SLE[54]; in post-hoc analysis it appears especially beneficial for mucocutaneous and musculoskeletal manifestations.[60]

In people with active, new onset or flare of Class III/IV (±V) LN on treatment with MPAA, we conditionally recommend a target MMF dose of 2–3g/d (or equivalent).

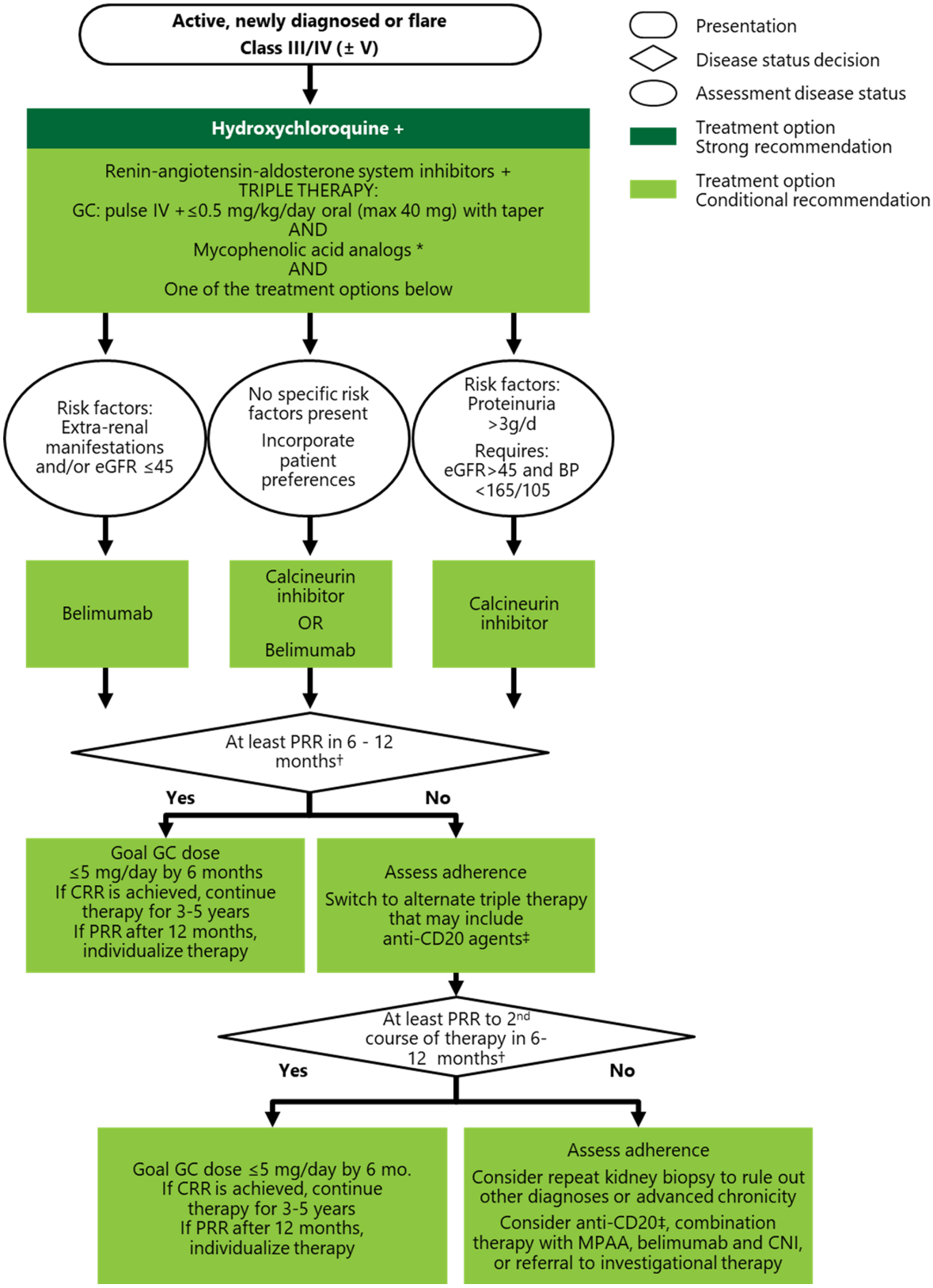

Figure 1. Recommendations for the treatment of class III, IV with or without class V lupus nephritis. * = Alternative triple therapy: glucocorticoids and Euro-Lupus Nephritis Trial low-dose cyclophosphamide and belimumab with mycophenolic acid analogs substituted for cyclophosphamide after the cyclophosphamide course is completed. Mycophenolic acid analogs regimens are preferred over cyclophosphamide regimens. † = Treatment should be escalated or changed earlier, even at ≤3 months, in patients with rapidly declining GFR or increasing proteinuria due to risk for potentially irreversible damage. ‡ = Rituximab, obinutuzumab, or others.

The dose of MPAA should be tailored to the individual patient, balancing the considerations of tolerability, safety, and efficacy. For pediatric patients, the usual starting dose is 1.2–1.4 g/m^2/d; mycophenolic acid levels may aid in tailoring dosage.

In people with active, new onset or flare of Class III/IV (±V) LN receiving a CYC-based regimen, we conditionally recommend the ELNT low-dose CYC regimen over a high-dose monthly pulse IV CYC regimen; we strongly recommend the ELNT low-dose CYC regimen over a daily oral CYC regimen.

An RCT and post-hoc analysis demonstrated that the ELNT regimen of CYC was as effective as intravenous monthly, high-dose CYC in achieving renal response.[61,62] The ELNT regimen is favored because of its better tolerability and toxicity profile, including a lower risk for infertility. Although pediatric data are limited to non-randomized, observational studies, the use of the ELNT regimen is preferred given the potential for multiple CYC courses over time.[63] The Voting Panel unanimously preferred an intravenous regimen over a daily oral CYC regimen because of the cumulative toxicities associated with oral CYC. It is important to provide fertility protective therapies to women and men of reproductive age when using a CYC-based regimen, particularly with high-dose pulse monthly IV CYC or >1 course of the ELNT CYC regimen.

In people with new onset or flare of Class III/IV (±V) LN who have undergone triple immunosuppressive therapy (pulse intravenous glucocorticoids 250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus either MPAA plus belimumab, MPAA plus CNI, or CYC plus belimumab) and achieved a complete renal response, we conditionally recommend continuing the same immunosuppressive regimen.

In people with active, new onset or flare of Class III/IV (±V) LN who have undergone triple immunosuppressive therapy with pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, plus either MPAA plus belimumab, MPAA plus CNI, or CYC plus belimumab) and achieved a partial renal response (PRR), we conditionally recommend individualizing therapy depending on clinical factors that include the trajectory of response.

If the patient with PRR is improving with reduction in proteinuria and increasing/stabilization of eGFR, the Voting Panel concurred that continuation of the initial triple immunosuppressive regimen with continued glucocorticoid taper is reasonable. However, if the patient shows indications of worsening disease activity (increasing proteinuria, worsening eGFR), we suggest altering therapy. A repeat kidney biopsy may be helpful to clarify proteinuria etiology (ongoing activity versus fixed damage). A specific duration of therapy is not recommended due to variability in clinical presentations.

In people with new onset or flare of Class III/IV (±V) LN who have undergone dual immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a complete renal response, we conditionally recommend continuing therapy with MPAA over switching to azathioprine (AZA).

People planning pregnancy or intolerant of MPAA should be treated with AZA.

In people with new onset or flare of Class III/IV (±V) LN who have undergone dual immunosuppressive therapy (glucocorticoids plus either CYC or MPAA) and achieved a partial renal response, we conditionally recommend escalating therapy to a triple immunosuppressive regimen.

Class V LN:

Class V (membranous) LN accounts for 20% of cases and is characterized by the presence of global or segmental subepithelial immune complex deposits. Class V LN can occur in isolation or in combination with Class III/IV.[64–68] There is limited evidence for management of pure Class V.

In people with active, newly diagnosed or flare of pure Class V lupus nephritis with proteinuria ≥1 g/g, we conditionally recommend treatment with a triple immunosuppressive regimen consisting of glucocorticoids (pulse intravenous glucocorticoids (250–1000 mg methylprednisolone daily × 1–3 days) followed by oral glucocorticoid (≤0.5 mg/kg/day, maximum dose 40 mg/day) taper, and MPAA plus CNI (over MPAA plus belimumab or CYC plus belimumab).

Post-hoc analyses from clinical trials support that voclosporin, but not belimumab, added to MPAA and low-dose glucocorticoids achieve earlier reductions in proteinuria in pure class V LN.[69] Alternative regimens include initial therapy with glucocorticoids and MPAA, CNI, CYC, azathioprine, or anti-CD20 therapy[65–68] (Figure 2).

The importance and optimal dosing of glucocorticoid for Class V LN is not certain, as suggested by the conditional nature of this recommendation. The Voting Panel opted to include pulse/oral glucocorticoid therapy with taper plus two immunosuppressive agents here based on improved outcomes in recent pivotal clinical trials of triple therapy[13,14] that included individuals with pure Class V. The certainty of the level of evidence was very low (due to indirectness). Glucocorticoid therapy, sometimes at very high dose, has been used consistently across prior trials that included participants with pure Class V in addition to Class III/IV LN. An RCT of pure Class V (single versus dual) therapies did not support benefit of glucocorticoid monotherapy[64] but showed the combination of prednisone plus CNI or CYC to be more effective than prednisone alone. While we may be able to use lower doses of glucocorticoids for pure Class V than for Class III/IV, we do not have high-level data to inform different dosing levels for Class V vs. III/IV. Clinician-patient discussion should guide

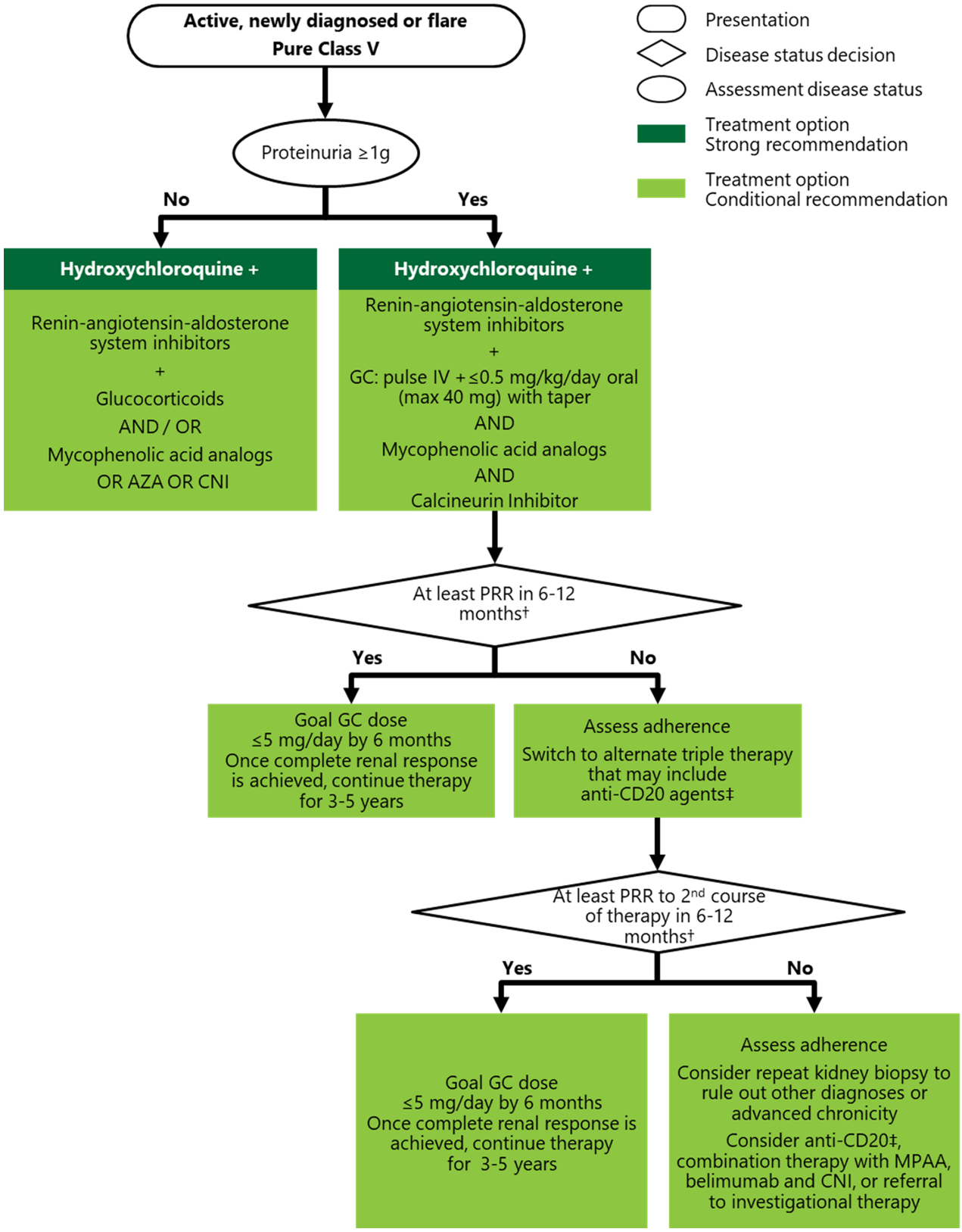

Figure 2. Recommendations for the treatment of pure class V lupus nephritis. † = Treatment should be escalated or changed earlier, even at ≤3 months, in patients with rapidly declining GFR or increasing proteinuria due to risk for potentially irreversible damage. ‡ = Rituximab, obinutuzumab or others. AZA, azathioprine; CNI, calcineurin inhibitors; GC, glucocorticoid; GFR, glomerular filtration rate; kg, kilogram; mg, milligram; MPAA, mycophenolic acid analogs; PRR, partial renal response.

therapy decisions, including the lack of high-quality data, the clinal presentation, and the patient's values and preferences.

In people with active, newly diagnosed or flare of pure Class V lupus nephritis with proteinuria <1 g/g, we conditionally recommend treatment with glucocorticoid and/or immunosuppressant therapy (MPAA, AZA, or CNI) over no glucocorticoid or immunosuppressive therapy.

The Voting Panel acknowledged the paucity of high-quality evidence for the treatment of Class V with low-level proteinuria because such patients were not included in clinical trials but expressed concern that low-grade proteinuria might progress to proteinuria >1g/g that could be less responsive to treatment.

Inadequate renal response/refractory LN

GPS: Medication dose and patient adherence should be assessed regularly throughout the course of treatment as an important first step in evaluating inadequate response or refractory LN, as insufficient treatment is a key cause of non-response.

Discussion regarding barriers to adherence (e.g., cost, side effects) is an important first step; strategies to monitor adherence (e.g., medication levels) may also be helpful.[70]

In people with any LN class with inadequate renal response (i.e., have not achieved at least a partial renal response by 6–12 months), we conditionally recommend escalation of treatment:

- **For initial dual therapy: escalate to triple therapy (glucocorticoids plus either MPAA plus belimumab, MPAA plus CNI, or ELNT CYC plus belimumab)**.
- **For initial triple therapy: change to an alternative (listed) triple therapy or consider addition of an anti-CD20 agent to MPAA or ELNT CYC**.

There are limited uncontrolled data[71–75] to guide therapy – including optimal timing – for inadequate renal response. Choice of therapy in the setting of inadequate response varies depending on several factors including the medication used initially, patient and clinician preference, and tolerability. Close monitoring is essential: treatment should be escalated or changed earlier, even at ≤3 months, in patients with rapidly declining GFR or increasing proteinuria due to risk of potentially irreversible damage.

In people with any LN class with refractory disease (ie, failed two standard therapy courses), we conditionally recommend treatment escalation to a more intensive regimen, including the addition of anti-CD20 agents, combination therapy with three non-glucocorticoid immunosuppressive agents (ie, MPAA, belimumab and CNI), or referral for investigational therapy.

When refractory LN is diagnosed, one may consider a kidney biopsy to assess the extent of chronic damage and determine whether escalating therapy is warranted. In cases of true refractory LN, meta-analyses suggest that 50–80% of patients convert to partial or complete responders with rituximab.[76,77] Other B cell targeted approaches,[78–80] as well as combination B cell therapies,[81–83] show utility in refractory LN and may offer future therapy options. (See Figure 3 for a Treatment Overview.)

Other lupus kidney disease

GPS: Alternative etiologies of kidney dysfunction in people with SLE should be carefully excluded, including non-inflammatory etiologies such as hypertensive, diabetic, and medication-induced nephropathy.

Less common manifestations of lupus kidney disease include thrombotic microangiopathy (TMA), Class II LN, and lupus podocytopathy. These were discussed by the Voting Panel but not formally voted upon given their lower incidence relative to Classes III/IV and V LN. The 2024 KDIGO clinical practice guideline for the treatment of lupus nephritis[84] provides details regarding clinical presentation and suggested management for these less common lupus kidney issues.

TMA

TMA is a histopathologic finding indicative of endothelial injury. Underlying causes include acute antiphospholipid antibody (aPL) nephropathy,[85] thrombotic thrombocytopenic purpura, complement-mediated TMA, and others. Because these conditions require different treatments, accurate diagnosis is important and often requires hematology consultation. While there was insufficient consensus to form a recommendation regarding aPL nephropathy or other TMAs in the context of LN, there have been reports of treatment with anticoagulation, plasma exchange, or C5 inhibitor therapy in this situation.[86,87]

Class II LN

Class II (mesangial) LN is characterized by expanded matrix with immune complexes confined primarily to the mesangium. Extensive podocyte effacement suggests lupus podocytopathy.[88]

The Voting Panel did not reach a consensus to formulate a recommendation for treatment although RAAS-I therapy is usual; however, repeat biopsy to assess for class switch or lupus podocytopathy may be considered in the setting of increasing proteinuria noted on follow-up.

Lupus podocytopathy

Podocytopathy usually presents with nephrotic range proteinuria; electron microscopy shows diffuse podocyte foot process effacement without subepithelial or subendothelial deposition.[89] Glucocorticoid and other immunosuppressive

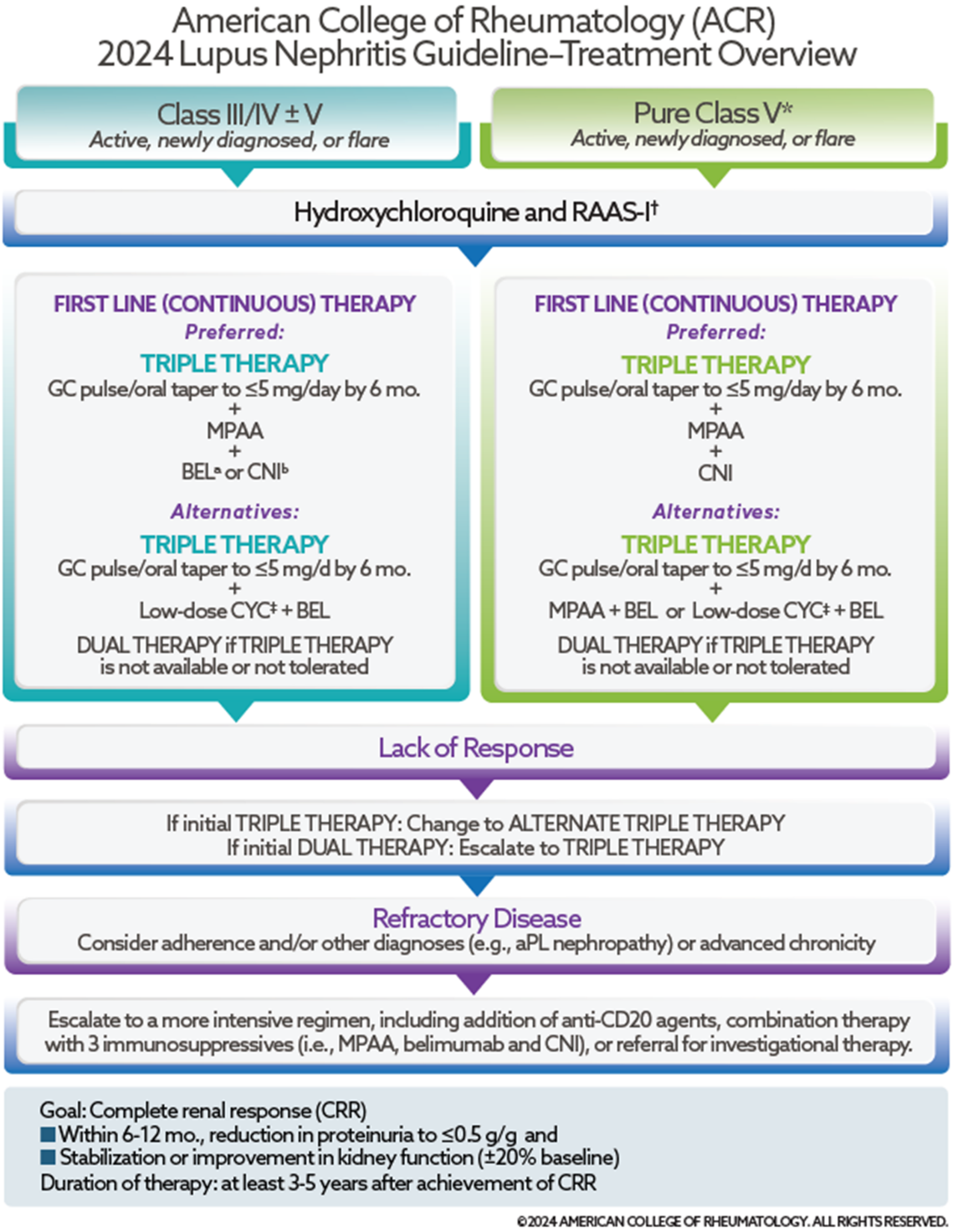

Figure 3. American College of Rheumatology 2024 Lupus Nephritis Guideline treatment overview. * For ≥1 gm protein; for <1 gm, treat with GC and/or immunosuppression. † Discuss adjunctive treatment with systemic anticoagulation with nephrology for patients with LN and significant factors for thrombosis (eg, low serum albumin in context of severe proteinuria). ‡ Substitute MPAA once low-dose CYC cycle is completed. a: Recommended preferentially when significant extrarenal manifestations are present. b: Recommended preferentially when proteinuria is ≥3.0 gm. GC pulse/oral taper: pulse intravenous GCs (250–1,000 mg methylprednisolone daily for 1–3 days) followed by oral GC ≤0.5 mg/kg/day (maximum dose 40 mg/day) and taper. Low-dose CYC: as per Euro-Lupus Nephritis Trial protocol,[61] 500 mg IV CYC every 2 weeks for 6 doses. Dual therapy: GC plus/oral taper plus one immunosuppressive agent, usually MPAA or low-dose CYC. RAAS-I, renin-angiotensin-aldosterone system inhibitors; GC, glucocorticoid; MPAA, mycophenolic acid analogs (including mycophenolate mofetil [MMF]; BEL, belimumab; CNI, calcineurin inhibitor; CYC, cyclophosphamide.

treatments are common[90]; therapy is best managed in collaboration with nephrology colleagues.

Adjunctive / non-immunologic treatments and good practice guidance

GPS: Adjunctive and non-immunologic therapies and practices should be added to appropriate immunosuppressive therapy to improve overall kidney health.

In addition to non-immunosuppressive kidney therapies such as RAAS-I, management of cardiovascular health, bone health, infection risk, and reproductive concerns should be addressed as summarized in Table 4.

GPS: In children with childhood-onset SLE (cSLE) nephritis, glucocorticoid regimens should use pediatric-appropriate doses for children, as reduction of cumulative glucocorticoid dosing is critically important given the early age of cSLE onset and attendant comorbidities.

GPS: In children with cSLE nephritis, clinicians should monitor for delayed pubertal onset and decreased growth velocity that can result from disease activity and glucocorticoid treatment and consider referral to pediatric endocrinology if indicated.

GPS: For children with cSLE nephritis, a structured, intentional transition[91–94] from pediatric to adult rheumatology care is indicated to avoid poor outcomes during this vulnerable period.

GPS: For older people with LN, medication number, type, and dosage should be regularly assessed, given the risks of polypharmacy and age-related decline in GFR in this population.

Monitoring LN activity

Treatment trials in SLE measure proteinuria rather than albuminuria. The gold standard for assessing proteinuria, the 24-hour urine collection, is challenging to implement in clinical practice; random urine protein-to-creatinine ratios are usually adequate. The first void of the day sample[95,96] is the most accurate for the spot urine collection but may not be feasible. Unexpected results on random testing should be followed by a 24-hour collection, especially before any change in therapy.

In people with LN who have not achieved CRR, we strongly recommend quantifying proteinuria at least every 3 months.

In people with LN in sustained clinical renal remission, we strongly recommend quantifying proteinuria every 3–6 months.

These recommendations are strong despite a lack of high-certainty evidence because in people undergoing treatment for LN who have not achieved complete renal response, quantifying

Table 4. Good practice guidance: adjunctive therapies for patients with lupus nephritis*

General considerations		Guidance
Kidney health: Non-pharmacologic	Diet	Limit sodium intake (suggest ≤2g sodium/day) Avoid high protein intake if eGFR <60 (suggest <1g/kg/day)
Kidney health: Pharmacologic	RAAS-I	Recommended for all LN patients, if tolerated
	SGLT2-I	Consider for stable LN patients with DM, CKD, moderate-high proteinuria, or heart failure (use with caution in patients on high-dose immunosuppression due to increased risk of urinary tract infection)
Cardiovascular health	Lifestyle	Avoid smoking, exercise, optimize BMI
	Blood pressure	Systolic BP <120 if tolerated
	Lipid management	Dyslipidemia management per CVD risk reduction guidelines
	CVD risk assessment	Estimate 10-year cardiovascular risk using a validated risk tool
Bone health	Screening and treatment	See ACR Glucocorticoid-induced Osteoporosis Guideline[125]
Infection	Screening	Screening for hepatitis B, hepatitis C, and tuberculosis
	Vaccination	See ACR Vaccine Guideline[126]
	Prophylactic therapies	Consider prophylaxis for PJP and hepatitis B when indicated
Reproductive health	Contraception	See ACR Reproductive Health Guideline[127] Use highly effective method (eg, IUD) If on MPAA, use IUD or two other forms
	Pregnancy	See ACR Reproductive Health Guideline[127] Contraindicated with active LN Azathioprine and tacrolimus are pregnancy-compatible: use when LN is in remission but ongoing treatment is required
	Fertility	See ACR Reproductive Health Guideline[127] Gonadotropin releasing hormone agonist co-therapy recommended in females treated with CYC. Consider IVF for oocyte/embryo cryopreservation if stable disease still requiring ongoing teratogenic therapies and concern for age-related infertility

* ACR, American College of Rheumatology; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; CYC, cyclophosphamide; DM, diabetes mellitis; eGFR, estimated glomerular filtration rate; IVF, in vitro fertilization; IUD, intrauterine device; LN, lupus nephritis; MPAA, mycophenolic acid analogs; PJP, pneumocystis jirovecii pneumonia; RAAS-I, renin-angiotensin-aldosterone system inhibitors; SGLT2-I, sodium-glucose cotransporter-2 inhibitors.

proteinuria every three months may prompt adjustment of treatment regimen. In people with LN who have sustained complete renal response, quantifying proteinuria every 3–6 months will minimize the risk of missing an LN flare that would require more aggressive treatment. While we are certain about the beneficial effects of monitoring and screening for proteinuria in both diagnosis and prognosis, there is a lack of evidence regarding the optimal screening interval, and the overall certainty of the evidence is very low. The benefit of potentially preserving long-term kidney function far outweighs the minimal risk of obtaining a urine sample.

GPS: For people with LN, serum complement and anti–double-stranded DNA (dsDNAAU: Expanded version of dsDNA was added before acronym at first mention in manuscript.) antibody should be measured at every clinic visit (but not more frequently than monthly).

While hypocomplementemia and elevated anti-dsDNA antibodies have only modest sensitivity and specificity for LN activity, several studies[97–99] suggest they may herald new onset LN or LN flare. Changes in these levels should prompt careful clinical and laboratory assessment but should not necessarily trigger preemptive treatment in the absence of clinical manifestations, unless previous individual clinical experience suggests otherwise. Anti-C1q antibodies[100] correlate better with LN flares[101,102]; however, this antibody testing may not be universally available. Emerging biomarkers' utility will be reviewed for future guideline updates as these become validated.

Renal replacement therapies (dialysis and transplant)

GPS: Decisions for initiation and type of dialysis and timing of kidney transplant require close collaboration with nephrology.

Ten to twenty-two percent of people with LN will develop ESKD.[2,3] Treatment options include hemodialysis or peritoneal dialysis, or a kidney transplant. Individual patient characteristics and preferences should impact dialysis modality choice. People undergoing peritoneal dialysis have a higher risk of infections, especially peritonitis. Hemodialysis has inherent complications – bloodstream infections and thrombosis – related to vascular access. People with antiphospholipid antibodies are at higher risk of vascular access complications and allograft thrombosis.[103,104]

In people with LN and ESKD, we strongly recommend kidney transplantation over dialysis without kidney transplantation.

Transplantation significantly reduces mortality, cardiovascular disease events, infections, and risk of flares compared to dialysis.[105] The Patient Panel highlighted both the poor quality of life associated with dialysis and the challenges of accessing transplantation. People with ESKD due to LN are less likely to receive a kidney transplant compared to people with other glomerulonephritides.[106]

In people with LN who have progressive loss of kidney function and are nearing ESKD (defined as an eGFR of 15 ml/min/1.73m^2), we conditionally recommend preemptive kidney transplant over dialysis/no preemptive kidney transplant.[107]

Preemptive kidney transplantation improves survival compared to non-preemptive approaches in people with CKD,[108,109] and an observational study suggested that preemptive kidney transplantation improves survival in people with LN compared to non-preemptive approaches.[110] The Voting Panel emphasized the benefits of avoiding dialysis morbidity but recognized transplant access limitations.

In people with LN and ESKD, we conditionally recommend proceeding with kidney transplantation without requiring complete clinical or serologic remission of SLE, provided there is no other major organ involvement.

Limited data indicate that lupus activity does not significantly affect allograft function.[111] The Voting Panel emphasized that transplant eligibility should not be based on serologic activity as it does not appear to have an impact on transplant outcome.[112] The recurrence of LN in the allograft is rare (10%) and often mild, with predominantly mesangial lesions.[113]

In people with LN on current dialysis or after kidney transplantation, we strongly recommend regular follow up with rheumatology.

Despite a low recurrence rate of LN in transplanted kidneys, regular rheumatology follow up is recommended even for people with SLE who have ESKD or are post kidney transplant. The recommendation is strong despite low certainty of evidence supporting the benefit of regular rheumatology follow up, due to the essential role of rheumatologists in managing the broader health issues associated with lupus. At least 50% of people with ESKD due to LN in the US remain on immunosuppression[114]; those who are co-managed with a rheumatologist (≥2 rheumatology visits per year) have higher survival rates.[107]

DISCUSSION

Lupus nephritis is among the most common severe manifestation of SLE. In this guideline, we propose treatment with triple therapy (glucocorticoids plus two immunosuppressive medications) as the most desirable therapy for LN, preferring MPAA regimens over CYC regimens. We also propose a lower dose glucocorticoid regimen (after initial intravenous pulse) to minimize toxicity, with a prednisone goal of ≤5 mg/day by 6 months of therapy. These recommendations are conditional and require discussion between clinicians and patients because multiple factors impact therapy choice.

We do not specify a particular CNI because comparative effectiveness and safety studies are not available, and accessibility may dictate the choice of CNI. Ongoing monitoring is essential as long-term nephrotoxicity is an important concern with any CNI.

These recommendations apply to adults and children with LN. The Guideline Team analyzed pediatric-specific LN data when available, as LN affects up to half of individuals with cSLE.[115,116] Since cSLE LN treatment includes higher cumulative doses of glucocorticoids and CYC,[117] these recommendations propose corticosteroid regimens that differ from other pediatric-specific options.[118] While efficacy evidence for this change is indirect, it acknowledges pediatric-specific concerns regarding glucocorticoid effects on growth and pubertal development. We also emphasize the necessity of structured transition to adult rheumatology and nephrology care.[118–121] Despite recent improvements in LN outcomes, youth of historically marginalized groups remain at higher risk for ESKD and dialysis.[122,123]

Two major themes emerged from the Patient Panel discussion. First, shared decision-making is a dynamic, ongoing process influenced by the patient's values, individual disease course, stage of life, medication tolerance, efficacy, and side effects; as such, an individual patient's decisions regarding management evolve over time. Second, patients emphasized the importance for clinicians to recognize pill burden, discuss all medication options, and provide close monitoring with the shared goals of preservation of kidney function, overall health, and optimal quality of life.

Current gaps in the LN literature identified through our systemic literature review and evidence analysis helped to identify important areas of study for a future research agenda (Supplementary Materials 8), including new agents and strategies to improve outcomes for people with LN. During this guideline's manuscript preparation, a positive phase 3 trial reported that addition of the humanized anti-CD20 therapy obinutuzumab to standard therapy (glucocorticoid and mycophenolate mofetil) led to a significantly greater likelihood of complete renal response at 76 weeks than did standard therapy alone, although infectious risk (particularly COVID-19) was higher.[124] Further studies on this and other agents may lead to more targeted and effective LN strategies and will be reflected in updated revisions of this guideline.

With the development of this guideline, the ACR recognizes the key role of clinical rheumatologists in managing LN. Important goals of this guideline are to provide substance and direction for therapy decisions after clinician-patient discussions, and to encourage close working relationships between rheumatologists and nephrologists to enhance collaborative care.

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