

## **SUPPLEMENTARY MATERIALS 1: Methods**

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

#### ***Methodology Overview***

This guideline was developed following the American College of Rheumatology (ACR) guideline development process (<https://assets.contentstack.io/v3/assets/bltee37abb6b278ab2c/bltae11ca9142708dfa/clinical-practice-guideline-policy-procedure-manual.pdf>). This process includes the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)).<sup>1-4</sup>

#### ***Teams Involved***

A Core Leadership Team (9 members) met weekly to supervise the project and was responsible for confirming the scope and clinical (Patient/Intervention/Comparator/Outcomes – PICO) questions (see Supplementary Materials 2), coordinating with the Literature Review Team, overseeing the voting process, and drafting the manuscript. The Core Team, together with the Literature Review Team, comprised individuals with content and methodological expertise, and included a GRADE methodologist who advised on the process of developing and presenting the evidence and provided input on the quality assessment of evidence and summary of findings (SoF) tables (provided in Supplementary Materials 3).

An experienced librarian designed and conducted the search strategy with input from the Core Team members. The Literature Review Team (23 members) screened papers for relevance, assessed study quality, extracted data, computed pooled estimates of outcomes, graded the quality of evidence, generated an evidence summary for each PICO, and compiled an evidence report.

A Patient Panel was convened to discuss patient values and preferences related to outcomes, evidence, and drafted recommendation statements. The ACR solicited volunteers for the Patient Panel, collecting details regarding Lupus Nephritis disease experience, experience with therapies under consideration, and potential conflicts of interest. The Core Team reviewed the applications to select members for the Patient Panel including 2 patients to participate on the Voting Panel. The Voting Panel used the input from the Patient Panel meeting to help guide their votes in balancing tradeoffs between the harms and benefits of the alternative management strategies.

The Voting Panel consisted of 20 people, including adult and pediatric rheumatologists and nephrologists, a rheumatology physician assistant, and two patient representatives. The role of the Voting Panel was to vote on the drafted recommendation statements derived from the PICO questions, keeping the evidence report, their expertise and experience, and patient values and preferences in mind.

The ACR provided training for everyone involved in the development of this guideline, which included explanations of the ACR guideline process and GRADE methodology. See Supplementary Materials 4 for panels/team rosters.

### ***Patient Panel***

The Patient Panel, consisting of 2 adult men and 13 adult women who had been diagnosed with Lupus Nephritis (LN), was convened on July 16, 2024. Dr. Mary Beth Son, Dr. Linda Hiraki (members of the Core Team), Dr. Shivani Garg (member of the Literature Review Team), and Amy Turner (ACR staff lead) facilitated the four-hour webinar discussion. The participants were first presented with the background and scope of the guideline project. The Patient Panel discussed their personal experiences related to the questions being considered in the guideline, expressing their values and preferences with particular focus on tradeoffs between screening or treatment

options given. Two patients on the Voting Panel, who had been at the Patient Panel meeting, conveyed the patient panelists' values and preferences during the two-day virtual Voting Panel meeting held July 23-24, 2024.

### ***Disclosures and Management of Conflicts of Interest***

Per ACR policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) was required to disclose all relationships (<https://assets.contentstack.io/v3/assets/bltee37abb6b278ab2c/blt547bd2adee41a8b7/lupus-guideline-disclosure-summary-2025.pdf>). Disclosures were evaluated to determine if any relationships were considered potential conflicts of interest for this project. Individuals whose primary employment (>51% of work time/effort) was with a company that manufactured or sold therapeutics or diagnostics were not eligible to participate.

The project's principal investigator (PI), the Literature Review Team leader, and the majority of guideline development team members had no relevant conflicts of interest for the full 12 months before this project began, through the project's end. Intellectual conflicts, such as a prior publication or scientific presentation on lupus nephritis, were recognized as important and were required to be disclosed, but because they were ubiquitous, intellectual conflicts were not counted as conflicted toward the allowed threshold.

Participant disclosures were initially shared in the project plan that was posted online for public comment as the project began. Disclosures were updated and shared again with each project participant via email prior to the Voting Panel meeting and verbally at the beginning of the virtual Voting Panel meeting. Updated participant disclosures are included online with this manuscript and in the guideline journal publication.

### ***Scope and Target Audience***

The scope of this guideline included the development of evidence-based recommendations for clinicians who care for people with lupus nephritis, as the first part of a broader ACR lupus guideline project. The target audience for this guideline includes people with lupus nephritis and their health care providers. Derivative products may be developed in the future to facilitate implementation of this guideline to these audiences.

### ***Establishing Key Principles and PICO Development***

The Core Leadership Team collaborated with the Literature Review Team and Voting Panel members to develop the initial set of PICO-formatted clinical questions for the overall ACR lupus guideline project, including this lupus nephritis guideline, as well as identify prespecified outcomes that were considered critical for each PICO question (see Supplementary Materials 2). To accomplish this, the Core Leadership Team held weekly conference calls and also convened a virtual meeting of the Core Leadership Team, Literature Review Team, and Voting Panel in which the scope of the guideline and PICO questions were discussed. The project scope and PICO questions were posted for 30 days on the ACR website for public comment and were then finalized.

### ***Framework for Development of this Guideline***

**Population:** The population of interest included people with LN regardless of age, gender, racial/ethnic background, or other demographic variables.

**Interventions:** Interventions included both medical therapies and procedures.

*Medical therapy interventions* included (alone or in combination and in various doses/regimens) glucocorticoid (intravenous and oral), renin-angiotensin system inhibitors, mycophenolic acid analogs, cyclophosphamide, calcineurin inhibitors, belimumab, azathioprine, anti-CD-20 therapies, and anticoagulant therapies.

*Procedures* included percutaneous kidney biopsy with histopathology, urinary proteinuria monitoring, and renal replacement therapies (hemodialysis, peritoneal dialysis, kidney transplant).

Interventions that were not included due to limitations in scope included medical therapy for aPL kidney disease and transplant, and management of important comorbidities for patients with LN such as infection screening and prophylaxis, vaccinations, cardiovascular screening, osteoporosis screening, and reproductive health concerns.

**Outcomes:** Critical outcomes included the following:

*For kidney biopsy:* Additional or different kidney diagnosis (e.g., thrombotic microangiopathy, acute tubular necrosis, class change, diabetes mellitus or arteriosclerosis/arteriolosclerosis) that impacts decision for and choice of therapy, level of proteinuria, kidney function, LN flare, and end stage kidney disease (ESKD) (dialysis or transplant).

*For treatment regimens:* Level of proteinuria, preservation of kidney function, LN flares, ESKD (dialysis or transplant), cumulative corticosteroid dose, CRR (complete renal response), PRR (partial renal response), quality of life, SLE disease damage and mortality.

*For renal replacement therapy:* Quality of life, SLE flare, disease damage, mortality, hospitalization, graft survival and recurrent SLE in kidney graft.

**Adverse events:** Adverse events included medication- and procedure-related adverse outcomes, in addition to disease-related adverse outcomes above.

*Medication-related adverse outcomes* included fracture, hypertension, type 2 diabetes mellitus and infection (glucocorticoid therapy), infection, cytopenias (immunosuppressive regimens), depression/suicide (belimumab), > 30% reduction in eGFR (calcineurin inhibitors), bleeding (anticoagulation), retinopathy and cardiac toxicity (hydroxychloroquine), or other toxicities leading to discontinuation of therapy.

*Procedure-related adverse outcomes* included biopsy-related bleeding risk (including serious bleed requiring transfusion or hospitalization), dialysis-related infection, thrombosis and cardiovascular events, and transplant-related morbidity and mortality including graft failure.

### **STUDY DESIGN (includes only studies published in English language)**

For all PICO questions, we included randomized controlled trials or non-randomized studies (this included case-control studies). To capture adverse events, we considered open-label extension studies of RCTs and other longitudinal observational studies that focused on safety and tolerability. For PICO questions that focused on assessing the accuracy of screening tools, we included studies without an independent control group, specifically cohort and cross-sectional studies. We also reviewed existing systematic reviews and guidelines from other societies to confirm that we had identified and included all relevant references.

#### **Included:**

- RCTs, including
  - Open-label extensions of RCTs with placebo involved
- Non-randomized controlled studies, including
  - Cohort studies
  - Case-control studies
- Cross-sectional studies
- Longitudinal studies (focusing on safety and tolerability)
- Systematic reviews and guidelines from other societies

#### **Excluded:**

- Abstracts

- Case reports
- Narrative reviews
- Prevalence studies
- Economic studies, e.g., cost-effectiveness studies
- Drug adherence studies
- Studies of risk factors
- Non-English papers
- Studies with irrelevant population, interventions, or outcomes
- Animal studies

## ***Systematic Synthesis of the Literature***

### ***Literature Searches***

To identify relevant evidence for the PICO questions, a medical librarian, in collaboration with the Core Team, performed systematic searches of the published English language literature. OVID Medline and OVID Embase searches were performed from 1946 to November 13, 2023, and updated searches were performed June 10, 2024 (see Supplementary Materials 5). Searches were broad, covering the entire lupus guideline project scope (including but not limited to lupus nephritis, for this guideline).

### ***Study Selection***

DistillerSR software (<https://www.distillersr.com/products/distillersr-systematic-review-software>) was used to aid in screening the literature search results. Teams of two independent reviewers performed duplicate screening of each title and abstract with articles identified as potentially eligible passing to review of the full text. Eligible articles underwent full-text screening

by two independent reviewers. Selected manuscripts were matched to PICO questions. Included manuscripts that related to SLE, not lupus nephritis, were set aside for future guideline work. See Supplementary Materials 6 for details related to the study selection process.

### ***Data Extraction and Analysis***

Comparative data (e.g., from RCTs and nonrandomized comparative studies) for each lupus nephritis PICO question was extracted using previously piloted Excel sheets and then automatically imported into RevMan web software (<http://tech.cochrane.org/revman>). We assessed risk of bias for randomized clinical trials using the Risk of Bias in randomized trials (RoB 2) tool and using the Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) for nonrandomized comparative studies (<http://handbook.cochrane.org/>). We conducted meta-analysis using RevMan web software using the inverse variance method and a random effects model. For dichotomous, time-to-event, and continuous outcomes, they were reported as relative risks, hazard ratios, and mean differences with 95% confidence intervals, respectively. Conducting a formal assessment of publication bias (funnel plot) was not feasible because of the small number of studies included in each meta-analysis.

### ***Evidence Report Formulation***

RevMan files were exported into GRADEpro software to formulate a GRADE Summary of Findings (SoF) table for each PICO question,<sup>3</sup> when comparative studies were available. The quality of evidence for each outcome was evaluated by one literature review team member, then as needed was verified by the literature review leader (RAM) using GRADE quality assessment criteria<sup>4</sup> with discordance resolved by discussion. The resulting SoF tables were compiled in an evidence report (Supplementary Materials 3). The Core Leadership Team reviewed the evidence report and addressed possible evidence gaps prior to presentation to the Voting Panel.



While economic studies were excluded from formal review, we looked at these papers informally, for completeness. For the three that were relevant, their assessments of cost-effectiveness do not disagree with our clinical recommendations. One study<sup>5</sup> supports the cost-effectiveness of reducing glucocorticoid dose, which we recommend. The second<sup>6</sup> supports use of mycophenolate mofetil over azathioprine for proliferative lupus nephritis for maintenance therapy in terms of cost effectiveness; this is in line with our recommendations for lupus nephritis treatment. The third study<sup>7</sup> assesses cost-effectiveness of belimumab and voclosporin for lupus nephritis treatment in the US. This analysis supports use of belimumab, but it suggests "high uncertainty" about the cost-effectiveness of voclosporin. This finding is not specifically relevant to our treatment recommendations, however, as we do not specifically recommend any one particular calcineurin inhibitor (CNI); rather, we recommend CNI therapy (including voclosporin, tacrolimus, and cyclosporin) for the reasons cited in the manuscript (comparative effectiveness and safety studies are not available, and accessibility may dictate the choice of CNI).

### ***Moving from Evidence to Recommendations***

GRADE methodology specifies that panels make recommendations based on a consideration of the balance of benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences. Key to the recommendation is the trade-off between desirable and undesirable outcomes; recommendations require estimating the relative value patients place on the outcomes.

A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the Voting Panel is very 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, such as when the evidence quality is low or very low, or when the decision is

particularly sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision making. Good practice statements (GPS) were also formulated, where appropriate; these are actionable statements where the desirable effects clearly outweigh the undesirable effects of an intervention, or vice-versa, but where formal evidence grading is not necessary because the net benefit is considered sufficiently obvious.<sup>8</sup> GPS are ungraded and no formal rating of quality of evidence or strength of recommendation is given.

Judgments are based on the experience of the clinician panel members in shared decision making with their patients, on the experience and perspectives of the 2025 guideline Patient Panel members, and, to a considerable extent, on the results of discussion with the Patient Panel.

### ***Consensus Building***

The Voting Panel received the evidence report for review before it met to discuss and decide on the final recommendations. Individual online voting took place first, to ascertain initial consensus, followed by a 2-day, virtual webinar meeting of the Voting Panel, where they reviewed the evidence and provided votes on the direction and strength of each drafted recommendation. The webinar voting process was conducted using Poll Everywhere software ([www.polleverywhere.com](http://www.polleverywhere.com)). A 70% consensus was used as the threshold for making a recommendation; if 70% consensus was not achieved during an initial vote, the panel members held additional discussions before re-voting until at least 70% consensus was achieved.

Consistent with GRADE guidance, in some instances, the Voting Panel chose to provide a strong recommendation despite a low or very low-quality rating of evidence.<sup>2</sup> In such cases, a written explanation is provided describing the reasons behind this decision with reference to GRADE guidance on the matter.<sup>2</sup>

### ***Final Review and Approval of the Manuscript by the ACR***

In addition to journal peer reviews, the manuscript was reviewed by the ACR Guideline Subcommittee, ACR Quality of Care Committee, and the ACR Board of Directors. These ACR oversight groups did not make or mandate that specific recommendations be made within the guideline, but rather, served as peer reviewers.

### ***Moving from Recommendations to Practice***

These recommendations are designed to support health care providers who work with patients in selecting therapies. Health care providers and patients must take into consideration not only clinical phenotype and level of disease activity, but also comorbidities, response and tolerance of prior therapies, patient's values and preferences, and patient's functional status and functional goals in choosing the optimal therapy for an individual patient at the given point in treatment.

### **REFERENCES**

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