SUPPLEMENTARY MATERIALS 1: Methods

2025 American College of Rheumatology (ACR) Guideline for the Treatment of Systemic Lupus Erythematosus

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).[1-4]

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 (21 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 Systemic Lupus Erythematosus (SLE) 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 17 people, including adult and pediatric rheumatologists, a dermatologist, 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 1 adult man and 12 adult women who had been diagnosed with SLE, was convened on October 16, 2024. Dr. Mary Beth Son and 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 three-day virtual Voting Panel meeting held December 4-5 and December 10, 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 SLE, 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 includes the development of evidence-based recommendations for clinicians who care for people with SLE, as the second part of a broader ACR lupus guideline project. The target audience for this guideline includes people with SLE 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 SLE guideline, as well as identify prespecified outcomes that were considered critical and important 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 SLE 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) hydroxychloroquine, glucocorticoid (intravenous, oral, topical, and intralesional), mycophenolic acid analogs, cyclophosphamide, calcineurin inhibitors, belimumab, azathioprine, methotrexate, anifrolumab, anti-CD-20 therapies, abatacept, tocilizumab, Janus kinase (JAK) inhibitors,

anticoagulant therapies, chloroquine, dapsone, calcium channel blockers, pentoxifylline, colchicine, retinoids, thalidomide/lenalidomide, anti-IL-1, PLEX (plasma exchange), IVIG, non-steroidal anti-inflammatory drugs (NSAIDs), antiseizure therapy, antipsychotic therapy, non-immunosuppressive symptomatic nerve-directed therapy, and cognitive therapy.

Procedures included disease activity measures, disease damage measures, surgical intervention (valve surgery), pericardiectomy, PT/OT and splinting for Jaccoud's arthropathy, and symptomatic Raynaud's therapy with gloves, socks, and warmers.

Interventions that were not included due to limitations in scope included medical therapy for aPL-related complications, therapy for "type 2" SLE manifestations, and management of important comorbidities for patients with SLE such as infection screening and prophylaxis, vaccinations, cardiovascular screening, osteoporosis screening, and reproductive health concerns.

Outcomes: Critical outcomes included the following:

Outcomes for all sections: SLE Flare, disease damage (SLICC-SDI), SLE disease activity, mortality, comorbidities, quality of life, prednisone dose $\leq$ 5mg/day, discontinuation of steroid therapy, and cumulative steroid dose.

Hematologic-specific outcomes: WBC count (increase, decrease, or no change), infection, and life-threatening bleeds.

Neurologic-specific outcomes: Neurologic damage, functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability Index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire), cumulative glucocorticoid dose, optic nerve damage, vision, seizure activity, resolution of acute confusional state, resolution of psychosis, prevention of recurrent psychosis, resolution of mononeuritis multiplex, prevention of recurrent mononeuritis multiplex, improvement of small-fiber neuropathy, prevention of recurrent small-

fiber neuropathy, further decline in cognitive ability, improvement of stroke, and prevention of recurrent stroke.

Cutaneous-specific outcomes: Cutaneous disease activity, rate and amount of improvement of alopecia, and rate and amount of improvement of oral ulcers.

Serositis-specific outcomes: Resolution of pericarditis, prevention of pericarditis flares, prevention of pericardiectomy, prevention of chronic pericarditis (>6 months), resolution of pleural disease, quality of life, prevention of pleural disease flares, prevention of shrinking lung syndrome, and prevention of fibrothorax.

*Musculoskeletal-specific outcomes***:** Diagnosis of subclinical arthritis, arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function), joint damage, functional status, and function of affected joints (hand function measure).

Vasculitis-specific outcome: Reduction of vasculitis activity.

*Cardiac-specific outcomes***:** Reduction of myocarditis activity, size of the valvular vegetations, valvular dysfunction requiring valve replacement, and embolic disease related to vegetations (including stroke and TIA).

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

Medication- or procedure-related adverse outcomes: Fractures, infections, type-2 diabetes mellitus, cataracts, osteoporosis, adrenal insufficiency (glucocorticoid therapy), retinal toxicity and cardiac toxicity (hydroxychloroquine), infection and cytopenias (immunosuppressive therapy), >30% decrease from baseline eGFR (CNIs), depression/suicide (belimumab), bleeding (anticoagulation), GI symptoms (colchicine and NSAIDs), headache (IVIG), liver toxicity (retinoids), neuropathy and GI effects (thalidomide/lenalidomide), surgical complications (hand arthroplasty), and surgical adverse outcomes (surgery).

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 not addressing the defined 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, and September 25, 2024 (see Supplementary Materials 5). Searches were broad, covering the entire lupus guideline project scope (including but not limited to SLE, 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 lupus nephritis, not SLE, were set aside and used in the first phase of

this 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 SLE 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 (Supplementary Materials 3) for each PICO question,[3] 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 [4] 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 two that were relevant, their assessments of cost-effectiveness do not disagree with our clinical recommendations. One study [5] supports the cost-effectiveness of reducing glucocorticoid dose, which we recommend. The second study assessed cost-effectiveness of conventional immunosuppressive therapies for cutaneous lupus;[6] it does not include cost-effectiveness for biologic therapies, however. Cost for lenalidomide was estimated to be >100x the cost of the most expensive conventional therapy (cyclosporine). This analysis supports careful consideration for use of lenalidomide among conventional agents from the cost perspective; this complements our recommendation for lenalidomide use as a last-resort therapy for refractory skin disease from the purely clinical perspective, largely due to its side effect profile.

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.

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 3-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). 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. The review process prompted a re-vote for additional clarification of several recommendations to ensure the wording accurately conveyed the Voting Panel's intentions. 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.[7] GPS are ungraded and no formal rating of quality of evidence or strength of recommendation is given.

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.[2] In such cases, a written explanation is provided describing the reasons behind this decision with reference to GRADE guidance on the matter.[2]

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.

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