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Clinical Practice Guideline for Systemic Lupus Erythromatosus and Lupus Nephritis

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This is to certify that the doctoral study by

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has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
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Executive Summary: Clinical Practice Guideline

Clinical Practice Guideline for Systemic Lupus Erythematosus and Lupus Nephritis

by

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Summary

This project addressed the critical practice problem of delayed and inaccurate diagnosis of systemic lupus erythematosus (SLE), which has been linked to increased morbidity and mortality, particularly among marginalized populations. These diagnostic challenges have been recognized globally, with international research highlighting inconsistencies in care and the absence of standardized guidelines. Implementing inclusive and equitable clinical practice guidelines (CPGs) that consider social determinants of health, political determinants of health and actively involve diverse populations in research can play a crucial role in reducing racial disparities and improve outcomes for all lupus patients. Thus, the development of a CPG focused on diagnosis and treatment of SLE and lupus nephritis (LN) formed the primary purpose of the Doctor of Nursing Practice (DNP) project.

The practice focused question was: Will a CPG adapted from EULAR 2023 be accepted for implementation in practice by a panel of experts in SLE care management? To evaluate the quality of the newly released guideline, an appraisal using the AGREE II instrument was used. Seven members of an expert panel including clinical and administrative staff provided the review. The AGREE II tool was used for appraising and selecting the CPG adopted in this project. and the results were unanimous for adopting the Lupus CPG. Addressing the gap in practice to better manage SLE and prevent LN in vulnerable populations promotes and addresses diversity, equity and inclusion, and represents a significant positive social change.

Background

Prior to 2024, there were no formal CPGs for SLE or for the management of LN. In response to this gap, the American College of Rheumatology (ACR) issued a call for expert collaboration to develop evidence-based guidance. This culminated in the release of the first official CPG for lupus in December 2024. This project aligns with the DNP role by integrating clinical scholarship, evidence-based practice and leadership to address health disparities, drive quality improvement and advance social change in the rheumatologic care of lupus patients. SLE, a chronic autoimmune disease that disproportionately affects certain populations, leads to significant disparities in health outcomes. SLE significantly increases the risk of cardiovascular disease, which is the most common cause of death among patients. In the United States, SLE is a top 10 cause of death among Black/African American and Hispanic women aged 15-44 (American College of Rheumatology, 2024; Fanouriakis et al., 2024).

Lupus prevalence is three times higher in Black/African American and Native American populations compared to White individuals. Black/African American women with lupus die up to 13 years earlier than non-Hispanic White women with the disease. In England, Black individuals are eight times more likely to be hospitalized with lupus compared to their White counterparts. Health disparities in autoimmune diseases are exacerbated in clinical settings that do not incorporate social determinants and patient-centered approaches to CPG development and delivery of care. Promoting equitable inclusion of racial/ethnic minorities in clinical research and developing equitable practice guidelines free of bias can help reduce disparities in lupus outcomes.

The project aimed to produce a comprehensive, evidence-based CPG for lupus management within the clinic to prevent LN and reduce morbidity and mortality. The practice serves ethnic minorities such as African American and Hispanics who suffer disproportionately higher morbidity and mortality rates. Thus, surveillance and improved treatment of SLE patients can improve the quality of care by mitigating morbidity related to end stage renal disease (ESRD) as the CPG helps the clinician to clarify treatment approaches, improve quality, reduce disparities in identified vulnerable populations, decrease disease activity, reduce LN, and reduce incidences of ESRD in SLE patients.

The treatment strategies as advised by EULAR 2023 and ACR 2024 CPG guidelines for SLE and LN have served as key components of the CPG (American College of Rheumatology, 2024; Fanouriakis et al., 2024). Thus, the project question that guided the DNP project was: Will a CPG adapted from EULAR 2023 be accepted for implementation in practice by a panel of experts in SLE care management?

The literature search started with keywords *SLICC, SLE, systemic lupus erythematosus, lupus nephritis, lupus glomerular sclerosis in ethnic minorities, African American females and lupus nephritis, Hispanic females and lupus nephritis, lupus, clinical practice guidelines, lupus disease activity, racial disparity in lupus, mortality, morbidity, belimumab, mycophenolate,* and *Lupus Nephritis*. A comprehensive global search was conducted using Google to identify CPG pertaining to SLE and the research that supported its development. This search strategy yielded approximately 400 articles from located at PubMed, CINAHL, Embase, Cochrane Library, and Scopus. The articles were then narrowed down to 30, then 24, with the final count after faculty advisement to

15 articles including research studies were selected. Several were excluded as they did not meet the exclusion and inclusion criteria. The final list included 14 scholarly peer reviewed articles. (see Appendix A). There were six level I, two level II and six level III articles (Dang et al., 2022).

There were five randomized controlled trials (RCTs) and one RCT Systematic Review (SR) that consistently support immunosuppressive therapies like biologic DMARDs recently approved food and drug administration (FDA) for SLE and LN. Medications genetically engineered through monoclonal antibody technology called B cell stimulator inhibitors (belimumab) are recommended earlier for lupus and LN. The main theme is that multiple therapies are advised, and these treatment recommendations reduce morbidity related to renal manifestations up to 85% effective reduction in disease activity as compared to standard therapy (ACR, 2024; Furie et al., 2024; Gianfrancesco et al., 2021; Schlencker et al., 2022; van Vollen Houn et al., 2022; Ye et al., 2022).

This evidence discussed by the EULAR guidelines of 2023 has since been adopted by the ACR in November 2024. Crucial key points are: monitoring renal protein creatinine clearances minimally every 6 months, abstaining from glucocorticoids and using the lowest effective dose when medically indicated, measuring disease activity at every office visit, close surveillance for SLE flares and renal manifestations, recognizing populations at risk mostly for ESRD and special consideration in selection of treatment modalities, special concerns for polypharmacological adverse events, malignancies, super infections and full collaboration between rheumatology and nephrology community

(ACR, 2024; Furie et al., 2024; Gianfrancesco et al., 2021; Schlencker et al., 2022; van Vollen Houn et al., 2022; Ye et al., 2022).

The important take aways in these findings is that disease activity monitored by serologic markers such as Double Strand DNA (DsDNA), and proteinuria showed that histologic findings were not necessarily congruent with actual serologic markers and patient could have class III or V LN with seemingly normal serologic results. This is so important in understanding the pertinence of early detection and quality health care to lupus patients because 1 in 5 will experience renal manifestation and succumb to renal replacement therapies by year 10 (ACR, 2024; Furie et al., 2024; Gianfrancesco et al., 2021; Schlencker et al., 2022; van Vollen Houn et al., 2022; Ye et al., 2022).

Two studies most relevant to the SLE and LN CPG discuss the assessment tools needed to assign scores for disease activities in SLE patients. Being able to predict high disease activity is crucial in clinical deduction the likelihood of lupus flares because serologic markers can be deceiving in clinical renal manifestations (Anderson, 2024; Jesus et al., 2019; Jesus et al., 2024). Using the systemic lupus erythematosus disease activity index 2000 (SLEIDAI 2K) adds an opportunity for clinicians to pinpoint early need to add more aggressive therapies to the treatment regimen. Low activity is denoted as remission and scores generally are less than three; Moderate disease are scores up to six; and high disease activity is above six (Anderson, 2024; Jesus et al., 2019; Jesus et al., 2024).

Several subjective domains are collected at each visit along with historical serology testing for compliments, double-stranded DNA test (DsDNA), pyuria, fever, hematuria, headaches, strokes, myocardial infarctions, proteinuria greater than 0.5 gram per 24-hour urine, alopecia, lupus rash, pericarditis, hemolytic anemia, pleuritis, signs of cranial neuropathy such as Raynaud's syndrome, vasculitis, organic brain disease, seizure activity, psychosis, and dementia (Anderson, 2024; Jesus et al., 2019; Jesus et al., 2024). The higher prevalence of these domains indicates high disease activity and a step-up approach in treatment modalities is medically necessitated.

Level 3 articles carry the continued consistency in their evidence for the management of lupus patients, which clearly supports the regular assessment for disease activity at each office visit and adjusting therapy accordingly. Two staple medications lupus patients all should be on include Plaquenil and methotrexate or Arava (Cody et al., 2023; Fanouriakis et al., 2024; Gordon et al., 2018; Jesus et al., 2024; Mosca et al., 2010; Schlencker et al., 2022). The next two medications are B cell stimulator inhibitor and Mycophenolate or a CNI. In European studies, there are newer medication classes known as CD20s not readily available in the United States as of May 2025, and thus these represent inconsequential inconsistencies as it pertains to guidance. The European Medicines Agency has approved several medications for the treatment of LN known as obinutuzumab (Gazyva/Gazyvaro) but not yet approved by the US Food and Drug Administration (Jesus et al., 2024).

Thus, studies at levels 1, 2, and 3 provide adequate support for the diagnosis of SLE, prevention and management of SLE and LN. Level 1 studies included the ACR with SR and six additional RCTs (ACR, 2024; Furie et al., 2024; Gianfrancesco et al., 2021; Schlencker et al., 2022; van Vollen Houn et al., 2022; Ye et al., 2022). Level 2 studies included rich detail on staging and scoring disease activity (Anderson, 2024; Jesus et al., 2019; Jesus et al., 2024). The level 3 studies provide adequate support for clinicians to manage treatment options (Cody et al., 2023; Fanouriakis et al., 2024; Gordon et al., 2018; Jesus et al., 2024; Mosca et al., 2010; Schlencker et al., 2022). Taken together, these studies lay important research groundwork on the diagnosis, treatment and management of SLE and LN (see Appendix A).

Clinical Practice Guideline Development

The CPG development began with selecting appropriate individuals and stakeholders to form the expert panel. These experts were selected because of their experience and qualifications in providing care to SLE patients. The panel included six stakeholders and one outside local clinician who practices in a competitor rheumatology clinic. The following individuals who were used as expert panel to help me adopt the proposed CPG. Further descriptions are provided below:

1. Chief Executive Officer: This individual has 20 years of experience in clinical and administrative duties in an area of rheumatology practice.
2. Chief Operational Officer- has 17 years of experience in clinical and administrative duties in rheumatology practice.
3. Staff Rheumatologist- A board certified physician with boards in internal medicine and rheumatology.
4. Medical Director- Internal Medicine (site preceptor). Board certified in internal medicine.

5. (LVN) Patient care coordinator patient facing and deals, referrals, secures prior auth for specialty pharmacy, assures that documentation meets medical necessity etc.
6. Nurse Practitioner -local area Rheumatology
7. Staff medical assistant & scribe- patient facing with several years of experience in caring for rheumatology patients in the practice.

The CPG consists of the lupus diagnostic flow chart, SLEDAI 2K disease activity assessment tool, the SLICC criteria assessment tool, and the algorithm for lupus and LN treatment protocol (See Appendix B). In addition, the evidence table with a summary of the literature was used (Appendix A). The materials formed the structure and evidentiary support for the CPG and were used to present to the expert panel. The review process followed the guidelines outlined in the AGREE II guidance (see Appendix C for actual questions on the Agree II instrument).

The expert panel reviewed all the CPG materials (the table of evidence, the CPG explanation, process flow chart) which were sent via email after a presentation was given and returned to project leader about a week later (see Appendix B). The AGREE Tool was completed by all seven expert panel participants within 2 weeks of presentation.

Results

The Agree II questions were grouped into six domains (see Appendix C). Each question on the Agree II instrument was measured on a 7-point Likert-type scale where 1 is equal to strong disagreement with the item and 7 equaled to strong agreement. Item scores were summed resulting in a domain score that would vary depending on the number of questions in the domain.

The answers from seven experts were compiled and reviewed. All scored Q1-23 with a 7 with two exceptions: Q18D5-The guideline describes *facilitators and barriers to its application*. One person scored as a 6, making the score for this question 6.83 of 7 or 97.6%. Q23D6- *Competing interests of guideline development* group members have been recorded and addressed. Three people scored this with a 6, making the score for this question 6.5 or 92.8%. All other questions were scored a 7, 100%. All respondents selected 7 for overall quality of the Lupus CPG and 7 for recommending without any modifications.

Two respondents provided qualitative descriptives to further show support for the CPG. The staff rheumatologist said that “The CPGs are useful for the clinical practice, will help clinicians to improve care in this patient population and are highly recommended.” The competing outside Rheumatology Practice Nurse Practitioner said, “The CPG was well developed; the questions and explanation was well attributed, and the population of target is well explained.”

A total of 11 individuals were eligible to complete the AGREE II appraisal within the organization. Of these, seven participants (64%) completed the full instrument. This exceeds the AGREE II Consortium’s recommended minimum of two to four independent appraisers, supporting the reliability and consistency of the appraisal findings. Respondents included both clinical and administrative stakeholders, offering a range of perspectives on the quality and applicability of the guideline. While the response rated is considered acceptable for a small organization, the limited number of respondents is acknowledged as a potential limitation, as it may have introduced response bias if nonparticipants held differing viewpoints.

While the appraisal relied on a limited number of participants due to the size of the organization, efforts were made to strengthen the methodological rigor. One key strength was the inclusion of an external clinician from a local unaffiliated rheumatology practice. This independent appraiser provided an unbiased perspective and helped mitigate potential internal bias. Their participation enhanced the credibility and generalizability of the appraisal findings, offering validation that the CPG holds value across varied care settings, including competitive outpatient environments.

The implementation of this CPG extends its impact beyond the local healthcare setting by contributing to a standardized approach for diagnosing and managing SLE and LN, particularly among high-risk populations such as African American and Hispanic women. As disparities in morbidity and mortality associated with LN are recognized globally, the adoption of evidence based guidelines supports broader health equity initiatives, informs national and international policy development, promotes consistency in clinical decision making across diverse care environments.

Conclusions

The unanimous appraisal of the CPG using the AGREE II instrument reflects strong consensus regarding its quality, relevance and applicability to practice. The literature consistently supports the need for standardized approaches to SLE and LN diagnosis, treatment and management especially in populations such as African American and Hispanic women who face disproportionate morbidity and mortality. To follow up on the usefulness of the CPG, a key recommendation to the site is to provide additional guidance on the use of the SLEDAI-2k scoring and the new classes of medications recommended. In addition, a quality improvement project at the practice is in order to evaluate full implementation and a change in practice at the site. The release of the 2024 ACR lupus CPG addresses a critical gap in care and provides a framework grounded in current evidence to reduce disparities. As a DNP scholar and clinician, my role in evaluating, translating and implement these guidelines is essential for driving quality improvement.

Locally, this work supports equitable care delivery and strengthens clinical decision making. Regionally and globally, the adoption of high quality guidelines fosters consistency across systems, contributes to policy advancement, and amplifies efforts to close outcome gaps in vulnerable populations. The alignment of this work with the DNP role highlights its potential to lead sustainable change in clinical practice and health outcomes on a broader scale. In particular, addressing the gap in practice to better manage SLE and prevent LN in vulnerable populations promotes and addresses diversity, equity and inclusion, and represents a significant positive social change.

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Appendix A

EBP Question:
Will a Clinical Practice Guideline (CPG) adopted from EULAR 2023 be accepted for implementation in practice by a panel of experts in SLE care management?

Article Number	Author and Date	Evidence Type	Sample, SampleSize, Setting	Findings That Help Answer the EBP Question	ObservableMeasures	Limitations	Evidence Level, Quality
1.	Anderson et al. (2024).	Level II Prospective data	Pilot study using lupus patients 239 sample Northwell Health and Feinstein Rheumatology Clinics by authors EA, CA, GF and MM between March 2018 and October 2020. All were aged ≥18 years and fulfilled the 1997 American College of Rheumatology (ACR) criteria.	Disease activity index, known as the SLEDAI 2K is useful for assessing disease activity as a outcome but does not have constitutional symptoms 1123 SLED-O, SLED-R, and PGA (physician global assessment) scores; 1066 PtGA (patient global assessment) scores.	Revised SlEDAI 2k score by addition of constitutional symptoms such as fatigue, fever, weight loss and lymphadenopathy only marginally improve the disease activity assessment. □ The revised index (SLED-R) replaced the fever descriptor with a constitutional descriptor including fever, fatigue, lymphadenopathy, and/or weight loss. □ SLED-R correlated more closely with PGA than SLED-O ($p < .001$). □ Fatigue was the constitutional symptom that contributed the most	More studies needed on use of other clinical indicators for disease activity in SLE. Fatigue, a subjective symptom, is difficult to attribute directly to SLE, raising concerns about its validity and inter-rater reliability. The study was limited by the pilot design and lack of broader clinical validation for SLED-R. Concordance between PGA and PtGA was lower when the constitutional descriptor was scored (55%) compared to not scored (72.5%).	Level II B : Moderate

					to higher PGA and PtGA scores (p = .001). The constitutional descriptor was scored in 45 subjects (18.8%) and 92 instances (8.1%), compared to the fever descriptor being scored in only 4 subjects (1.7%) and 5 instances (0.4%). Higher mean SLED-O and PGA scores were observed when constitutional symptoms were scored versus not scored (p < .002).		
\\\2	Cody et al., (2024).	Level III Retrospective Cohort	Sample size-165 Children and adolescents diagnosed with childhood-onset systemic lupus erythematosus (cSLE) Setting- Cincinnati Children's Hospital Medical Center, encompassing patients enrolled in the Cincinnati Lupus Registry between January 2008 and May 2021.	The study emphasizes a treat-to-target approach which quantifies the necessity to achieve low disease activity hoping to reduce organ damage. The study evaluated the applicability of the Lupus Low Disease Activity State (LLDAS) as a treatment target in cSLE and its association with reduced Renal damage About 80% of patients achieved LLDAS at	Low Disease Activity lupus indices. Achievement and maintenance of LLD Disease activity assessed using the SLE Disease Activity Index (SLEDAI-2K Damage accrual measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)	The limits are as follows: This was an observational study and not a Randomized study and the findings show associations not causation. Different treatment or medication were used and would affect the achievement of LLDAS There were no assessments for confounders such as	Level III B: Good

				least once during follow-up. There were challenges for certain patients with lupus nephritis to achieve LLDAS and they were less likely to sustain or reach remission ($p<0.03$). The median time to achieve LLDAS was longer for patients with LN ($p<0.0001$). Racial disparities exemplified by non-white patients requiring longer time to reach LLDAS was observed ($p=0.0013$) Pre-existing renal manifestation was a significant predictor of failure to maintain LLDAS ($p=0.0271$). In other words, they were at higher risk of accumulative damage with each flare even though they may reach LLDAS. 22% of patients who achieved LLDAS still acquired new damage. Patients with LN had a		medication adherence, lifestyle, social determinants of health and mental states. The criterial for LLDAS does not capture all aspect of disease activity	

				higher risk of new damage even if achieving LLDAS (p=0.04). Patients maintaining LLDAS for a higher proportion of follow-up time had reduced risk of new damage. The study suggests that LLDAS is a useful treatment target in cSLE, associated with reduced damage accrual.			
3	Fanouriakis et al., (2023)	Level III Clinical practice guidelines revised By EULAR	Task Force Team assembled by EULAR with panel of 35 Rheumatologist, five Nephrologist and two Patients	Consensus on several overarching principles for treating SLE patients. Hydroxychloroquine (HCQ) all lupus patients at a target dose of less than or equal to 5 mg/kg of real body weight/day balancing efficacy in preventing flares and minimizing the risk of retinal toxicity. Glucocorticoids (GC). Eular advocates for the lowest dose possible to control symptoms, with strategies to taper as soon as possible. Immunosuppressive drugs (ISDs)-	Comorbidly manifestations identified as constellations of disease activity in SLE; CPG aimed at reducing these provided.	Needed Development of new therapies, more training sites, more research by industry vs drug companies	Level III B: High

				methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, tailored to disease severity and organ involvement. Calcineurin Inhibitors (CNIs): Cyclosporine, tacrolimus, and cyclosporin are considered frug of choice for Lupus nephritis or refractory cases. Biologic Therapies: Belimumab and anifrolumab are advised with HCQ and either a MCC or CNI for high disease Activity based on serologic markers, histologic findings and or LLDAS. In patients contraindicated for these drug or with severe refractory disease, Rituximab is acceptable option.			
4	Gordon et al., (2018)	Level III CPG from the British of Columbia UK	Systematic Literature Review RCT	Aligns with Armamentarium approach of therapy based on disease activity.	Older than 2019; Newer drugs are using last resort.	More research needed on newer drug use.	Level III A: high

5	Jesus et al. (2024).	Level III Post Hoc study on use of Benlysta therapy for SLE	3-year g 52-week treatment periods of the phase III TULIP-1 and TULIP-2 trials and the 3-year open-label	Benlysta studied with placebo blind study in post hoc found to improve SLE DAS indexes.	This the first pilot study. SLE-DAS is a 17-item instrument designed to provide a practical, accurate, and sensitive measure of SLE disease activity, addressing limitations of previous assessment tools. The SLE-DAS can be calculated in approximately 1–2 minutes using an online calculator, enhancing its practicality in clinical settings. The SLE-DAS was designed to provide a continuous measure of disease activity in SLE patients, addressing limitations found in previous assessment tools. The score underwent rigorous validation in diverse cohorts, demonstrating its reliability and applicability across	More studies needed	Level III A: High

					various patient demographics. SLE-DAS exhibited high sensitivity in detecting changes in disease activity, making it a valuable tool for monitoring patient progress over time. The study established clear thresholds within the SLE-DAS to define clinical remission and low disease activity states, aiding clinicians in setting precise treatment goals		
6	Jesus et al. (2019).	Level II A longitudinal cohort study was conducted of 334 SLE patients during a 36-month follow-up	334 patients Cohort prospective study	SLEDAI 2K fail to detect disease activity alone. Major problem in clinical trials and daily practice.	At each outpatient visit, disease activity was scored using the Physician Global Assessment (PGA) and SLEDAI-2K. Correlations between PGA and SLEDAI-2K were assessed	More research needed. Better disease activity tool needed	Level II A: High
7	Mosca et al. (2019).	Level III Clinical Practice Guideline for	Delphi group discussion with team include rheumatologist, internist and	Guidelines need for standardization of SLE monitoring	Multiple indices are needed for assessment of SLE disease activity	More research needed	Level III A: High

		monitoring SLE patients	nephrologist; AGREE II tool				
8	Schlencker et al., (2022).	Level III	Cross sectional Qualitative study using patients, focus groups and health professionals	Clinical Practice Guidelines for SLE in France	framework to improve individual patient pathways in SLE was developed, discussed and validated during a consensus meeting with representative stakeholders	Region limitations	Level III A: High
9	Touma et al., (2024).	Level III	Qualitative data collection from 296 physicians reporting on 730 patients analysis of data from the Adelphi Real World Lupus Disease Specific Programmed™ (DSP), collected in the United States of America (USA) and Europe in 2010, 2013 and 2015, these data did not follow the same patients, but rather were comprised of three separate cohorts.	Clinical practice Guidelines clarify treatment and monitoring criteria for SLE patients	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Work Productivity and Activity Impairment-Lupus questionnaire (WPAI-Lupus) LDAS is defined as a SLEDAI score ≤ 4 (with no activity in renal, central nervous, gastrointestinal, or cardiopulmonary systems, and no vasculitis, fever, or hemolytic anemia), a SELENA-SLEDAI physician global assessment ≤ 1, receiving ≤ 7.5 mg/day glucocorticoid,	Due to the observational nature of the data, any significant difference observed in an outcome using a bivariate test between two groups (e.g., a t-test) may be due to confounding factors.	Level III A: High

					immunosuppressant or approved biologics only at well-tolerated standard maintenance doses, and demonstrating no new lupus disease activity compared with the previous assessment		
10	Ye et al. (2022)	Level I Randomized control Trial	Sample: Patients with type III + V or IV + V lupus nephritis. Sample Size: 56 patients divided into a treatment group (28) and a control group (28). Setting: The First Affiliated Hospital of Hainan Medical University, Haikou City, China.	Clinical analysis of multi-target treatment for complex lupus nephritis. The treatment group (multi-target therapy) showed a higher remission rate (85.2%) compared to the control group (57.7%) after 72 weeks. Adverse reactions were less frequent and milder in the treatment group.	Significant reductions in urine protein levels, SLEDAI scores, and ds-DNA antibody titers were observed in the treatment group.	Sample size and study design	Level I High to Moderate quality: A to B
11	Furie., Madan, A., & Roth, D. A. (2022)	Level I RCT	Sample: Patients with active lupus nephritis completing the BLISS-LN study's double-blind phase. Sample Size: 257 patients enrolled in the open-label phase (123 placebo-to-belimumab, 132	Belimumab showed an enduring safety and efficacy profile when combined with standard therapy for lupus nephritis. Primary efficacy renal response increased from 60% to 67% in the placebo-to-belimumab group and from 70% to 75% in	Urine protein-creatinine ratio (UPCR) and estimated glomerular filtration rate (eGFR) remained stable across the 28-week extension phase. Anti-dsDNA levels decreased, and	Open-label design lacked a placebo control, making statistical treatment comparisons difficult. The short duration of the extension phase (28 weeks) may not fully capture long-term efficacy and safety.	**Level I**. B: Moderate Quality

			belimumab-to-belimumab). Setting: Multicenter study across multiple international sites.	the belimumab-to-belimumab group. Complete renal response increased from 36% to 48% in the placebo-to-belimumab group and from 48% to 62% in the belimumab-to-belimumab group. No new safety signals were detected during the open-label phase.	C3/C4 complement levels improved, indicating biological response to belimumab. Biological Effects: Belimumab showed sustained biological activity, reducing inflammation markers such as anti-dsDNA antibodies and increasing complement levels. Clinical Relevance: Supports belimumab as an effective and safe therapy for lupus nephritis when combined with standard therapy.	Selection bias may exist, as patients completing the double-blind phase likely had better tolerance to belimumab.	
12	van Vollenhove (2020).	LEVEL I RCT Open label Phase III	Sample: Patients with systemic lupus erythematosus (SLE) from the BLISS-52 and BLISS-76 studies. Sample Size: 735 patients, with 368 completing the study. Setting: International multicenter sites; non-US patients.	Long-term belimumab use showed stable safety with no new safety signals over eight years. Organ damage progression was minimal; 87.7% of patients showed no change in the SLICC/ACR Damage Index score at study year 8. Annual incidence of	SLICC/ACR Damage Index: Mean score at baseline was 0.6 and remained stable with a mean change of 0.2 over eight years. Prednisone Use: Reduction in daily prednisone dose observed, with 67.8% of patients decreasing their dose to ≤7.5 mg/day by study year	Open-label design lacked a placebo group for comparison. Withdrawal rates (50.1%) could introduce responder bias. Study excluded patients with severe lupus nephritis or CNS disease, which may limit generalizability.	Level I Moderate quality: B

				adverse events (AEs), including serious AEs, remained stable or declined over time.	7. Adverse Events: Most common AEs included headache, nasopharyngitis, and diarrhea.		
13	American College of Rheumatology (2024)	Level I to III Evidenced Based Guidelines With 28 graded recommendations (7 strong, 21 conditional and 13 ungraded recommendations	**sample**: Recommendations apply to adults and children with lupus nephritis (LN). **Setting**: International guidelines designed for clinical implementation in collaboration between rheumatologists and nephrologists.	Recent data indicates that the age-adjusted mortality rate for SLE as an underlying cause of death is 0.64 per 100,000 for women and 0.12 per 100,000 for men. For this reason, ACR strongly recommend screening for proteinuria every 6–12 months or during extra-renal flares in SLE patients. Prompt kidney biopsy is advised for suspected LN or significant proteinuria (>0.5 g/g). Triple therapy (glucocorticoids + 2 immunosuppressive agents) preferred for active or severe LN (Class III/IV or V). Recommend prednisone taper to ≤5	Proteinuria levels monitored every 3–6 months for LN patients. Serum complement and anti-dsDNA antibody levels monitored at clinic visits. Glucocorticoid doses tailored to achieve ≤5 mg/day within six months.	**Limitations** Lack of direct comparative studies for some treatment regimens (e.g., CNIs). Accessibility of certain therapies (e.g., belimumab or calcineurin inhibitors) may vary by location and healthcare system. Prioritizes triple therapy for severe LN, emphasizes lower glucocorticoid doses to reduce toxicity, and encourages shared decision-making to align treatments with patient needs.	Level I through III High Quality: A With Expert Consensus to the EULAR Guidelines of 2023

				mg/day by 6 months and therapy duration of 3–5 years for sustained renal response. Individualized escalation of therapy for refractory LN, including anti-CD20 agents or investigational therapies			
14	Tian et al. (2023)	Level I Bayesian hierarchical linear mixed model systematic review of observational studies.	incorporating data from 112 studies spanning 32 countries. global setting, analyzing studies from various regions worldwide to estimate the incidence and prevalence of SLE.	Global Prevalence: The study estimated the global prevalence of SLE to be approximately 43.7 per 100,000 persons **Global Incidence:** The annual global incidence rate was found to be around 5.14 per 100,000 person-years **Regional Variations:** Significant regional differences were observed: **Highest Prevalence:** North America, with an estimated 241 per 100,000 persons.	The study utilized incidence rates (new cases per 100,000 person-years) and prevalence ra**tes** (total cases per 100,000 persons) to quantify the occurrence of SLE. Bayesian hierarchical linear mixed model was employed to estimate these rates, accounting for variables such as age, sex, diagnostic methods, and geographical regions.	Data Gaps: Approximately 79.8% of countries lack specific epidemiological data on SLE, leading to reliance on modeling for these regions Variability in Diagnostic Criteria: Differences in diagnostic methods across studies may contribute to inconsistencies in reported incidence and prevalence rates. **Potential Biases:** Variations in healthcare infrastructure and access could influence the detection and reporting of SLE cases, potentially	Level I A: high-quality

				Lowest Prevalence: Africa, with approximately 6.5 per 100,000 persons Gender Differences: SLE predominantly affects females, with a female-to-male ratio ranging from 2:1 to 15:1 across different regions Age Distribution: The highest incidence and prevalence rates were observed among individuals aged 50–59 years. Diagnostic Criteria Impact: Variations in diagnostic criteria and methodologies among studies contributed to differences in reported incidence and prevalence rate		affecting the accuracy of the estimates.	
15.	García-Ríos et al. (2022)	Level I Systemic Literature Review	The review included 15 studies published between 2012 and 2022, encompassing various study designs such as cross-sectional, case–control, and cohort studies.	studies investigated oral manifestations in patients diagnosed with SLE across different geographic locations. There is strong evidence that oral manifestations are common yet often overlooked in SLE	A significant proportion of SLE patients experience oral symptoms, with reported rates varying across studies. The most common manifestation appearing in 9% to	The inclusion of different study designs (cross-sectional, case–control, cohort) may introduce heterogeneity, affecting the comparability of findings.	Moderate B

				patients. Recognizing these symptoms early can aid diagnosis and improve patient outcomes through better interdisciplinary care and targeted treatments.	45% of SLE patients, depending on the study. Hyposalivation (Dry Mouth) – Many patients exhibited reduced salivary flow, increasing the risk of dental caries and oral infections. Glossodynia (Tongue Pain) – Some patients reported burning sensations or pain in the tongue, affecting eating and speech. Oral Pigmentation Changes – Darker pigmentation of the oral mucosa was observed in some SLE patients. Cleft Tongue and Cheilitis – Inflammatory conditions affecting the lips and tongue were also reported, though less frequently. Secondary Sjögren's Syndrome – Many SLE patients developed secondary	some of the studies exhibited moderate risk, potentially influencing the reliability of the results. Differences in diagnostic criteria and assessment methods across studies could lead to inconsistencies in reported oral manifestations Varied sample size and some region limited representation	

					Sjögren's syndrome, leading to severe dry mouth and eye symptoms. Temporomandibular Joint (TMJ) Arthritis – Jaw pain and difficulty in mouth opening were noted due to arthritis affecting the TMJ.		

Appendix B

Lupus Clinical Practice Guideline

Lupus diagnosis can be challenging because of the constellation of symptoms that can mimic other conditions; in the early stages of the disease, about 20% of the patients will have ANA titer true or false negative at various stages of the disease. It is the great masquerader. The immune system goes into a cytokine release storm and creates other conditions such as false positive syphilis test and HIV test, rendering this disease problematic to assess; thus, an index of high suspicion is needed, or the patient can be misdiagnosed. Even worse, a delay in diagnosis can lead to life-threatening and debilitating complications as this disease causes irreparable damage to multiple organ systems. The following is a list of steps in the Process flow chart for suspected Lupus in Figure 1. The next page shows the EULAR ACR SLICC criteria and the clinical and serologic domains for score calculation.

SLE Process Flow Chart List in diagnosing:

1. SLE suspected
2. Perform Laboratory Testing (Use Advise Panel)
3. ANA titer >= 1:80 is considered positive

It does not have to be sequential.
It is very common to have false negative ANA in the early stages
False positives can be caused by malignancies and other conditions

4. Apply the EULAR SLICC criteria for 2019

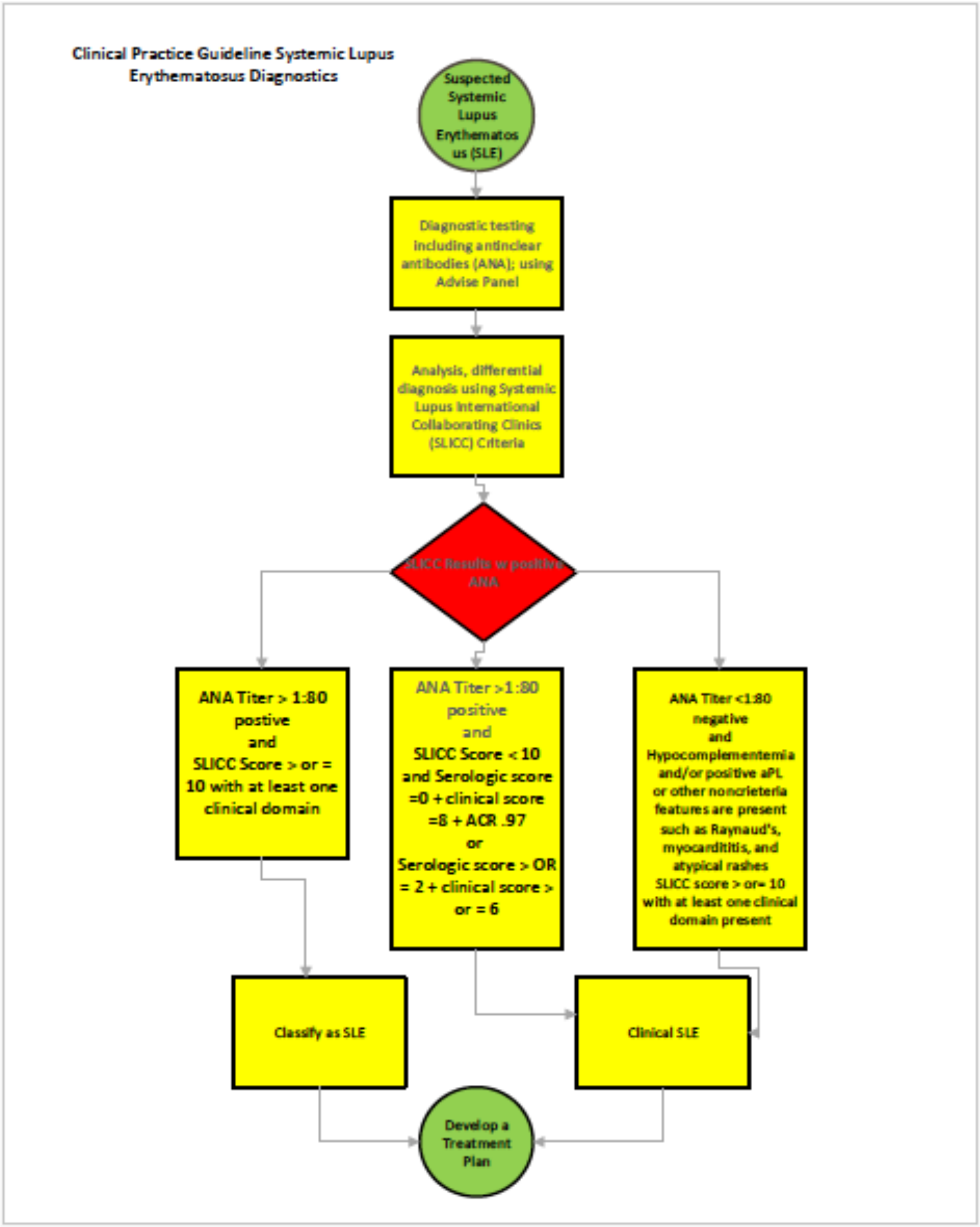
>or = 10 points with at least one clinical domain
Is classified as SLE

5. Even if the EULAR SLICC criteria 2019 score is less than 10,

Classify as clinical SLE if the score is less than or equal to 8 with
The presence of ACR 97 defined photosensitive rash without any
Immunological or serologic markers; or if there is a score of >or = 6
For clinical domains with two or more immunological points.

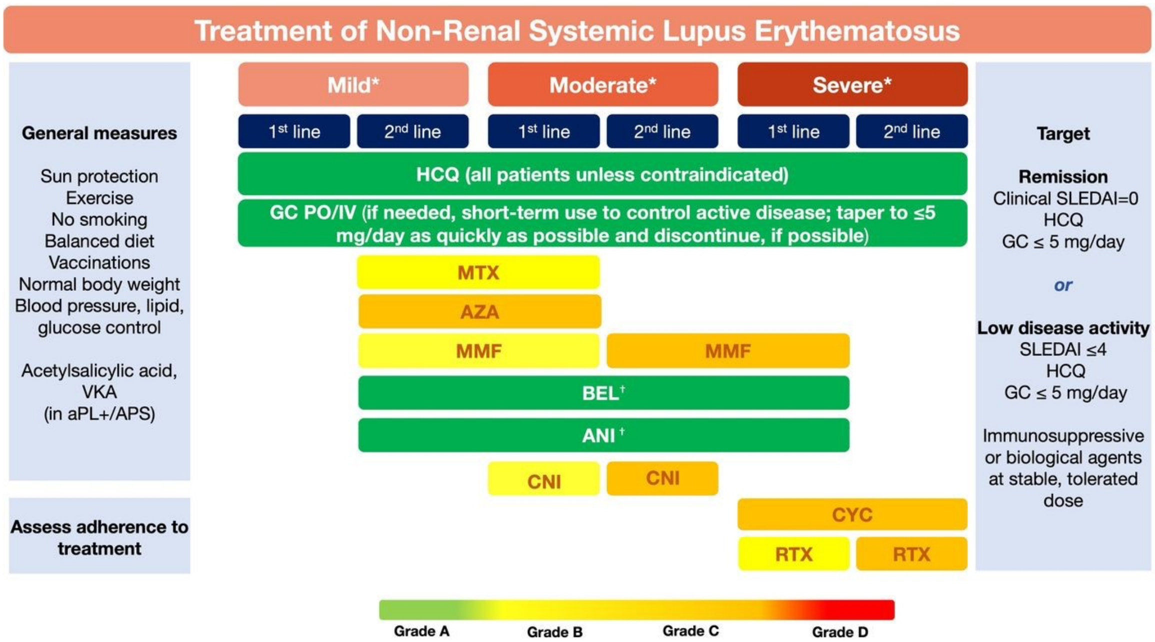
6. Patients with a negative ANA titer should be evaluated with alternative

Entry criteria such as scoring 10 points with at least one clinical criterion,
The presence of hypocomplementemia, or positive anticardiolipids (aPL).



Treatment Determination Based on Disease Activity

Lupus treatment is determined based on the disease activity. Using the SLEDAI 2K index tool below.
EULAR ACR Recommendations for Clinical Practice Guideline Treatment of SLE



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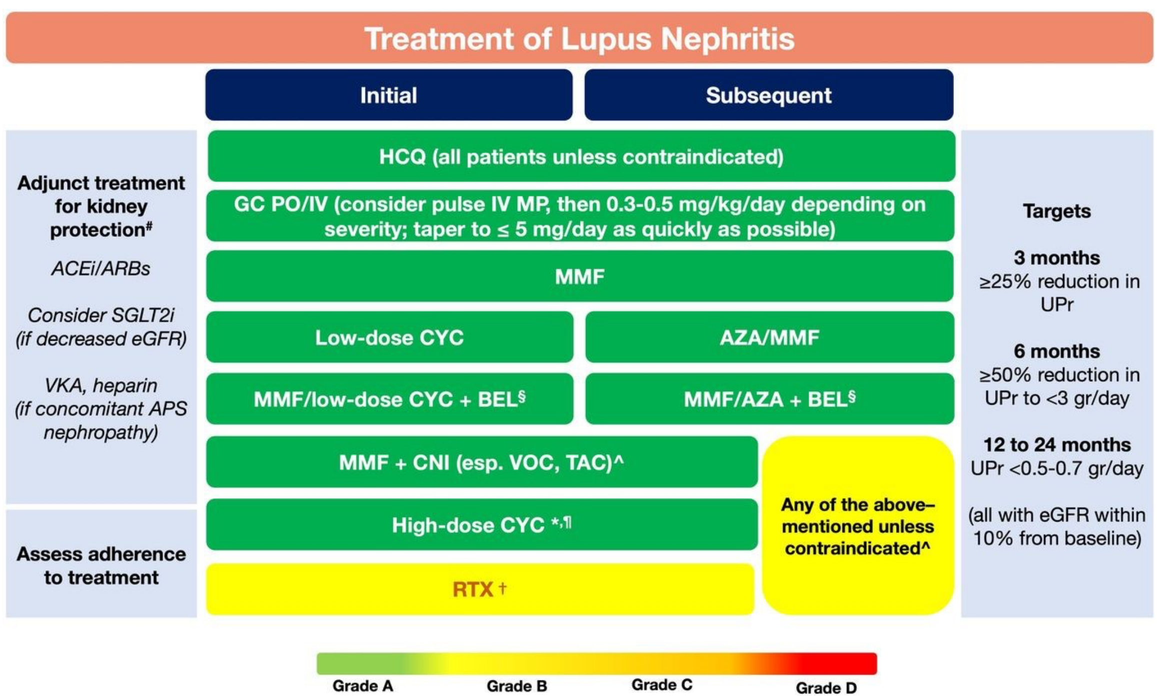
EULAR Guideline (2019) Treatment of non-renal systemic lupus erythematosus.

1. A top-to-bottom sequence does not imply an order of preference (e.g., MTX, AZA, and MMF are equal options for second-line therapy in mild disease or first-line therapy in moderate disease).
2. *Mild disease: constitutional symptoms; mild arthritis; rash ≤9% body surface area; platelet count (PLTs) 50–100 × 10^9/L; SLEDAI≤6; BILAG C or ≤1 BILAG B manifestation.
3. *Moderate disease: moderate-severe arthritis ('RA-like'; rash 9%–18% BSA; PLTs 20–50×10^9/L; serositis; SLEDAI 7–12; ≥2 BILAG B manifestations).
4. *Severe disease: significant organ-threatening disease (cerebritis, myelitis, pneumonitis, mesenteric vasculitis); thrombocytopenia with platelets<20×10^9/L; TTP-like disease or acute hemophagocytic syndrome; rash>18% BSA SLEDAI>12; ≥1 BILAG A manifestations.
5. The recommendation of belimumab and nivolumab as first-line therapy in severe disease refers to cases of extrarenal SLE with non-major organ involvement but extensive disease from skin, joints, and so on. Anifrolumab, as an add-on therapy for severe diseases, refers mainly to severe skin diseases.

6. For patients with severe neuropsychiatric disease, anifrolumab and belimumab are not recommended.

7. Abbreviation legend:
ANI, anifrolumab
aPL, antiphospholipid antibodies
APS, antiphospholipid syndrome
AZA, azathioprine
BEL, belimumab
BILAG, British Isles Lupus Assessment Group
CNI, calcineurin inhibitor
CYC, cyclophosphamide
GC, glucocorticoids
HCQ, hydroxychloroquine
IV, intravenous
MMF, mycophenolate mofetil
MTX, methotrexate
PO, per os
RTX, rituximab; SLEDAI, SLE Disease Activity Index
VKA, vitamin K antagonists

EULAR ACR Recommendation of Treatment for Lupus Nephritis



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EULAR Guidelines (2019) Treatment of Lupus nephritis

1. The top-to-bottom sequence does not imply an order of preference (similar to Figure 1).In addition to general protective measures, as outlined in Figure 3.
2. §BEL should always be given in combination with MMF or low-dose CYC as initial therapy and with MMF or AZA as maintenance therapy.
3. ˆCNIs should be given in combination with MMF. *Particularly recommended in poor prognostic factors: reduced eGFR, histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation.
4. ¶Extension of high-dose CYC to subsequent phase refers to severe LN cases, in which bimonthly or quarterly CYC pulses may be given following six-monthly pulses.
5. †In relapsing/refractory disease, especially after failure to CYC-based regimens.
6. Abbreviation Legend:

ACEi, angiotensin-converting enzyme inhibitors
APS, antiphospholipid syndrome
ARB, angiotensin receptor blockers
AZA, azathioprine
BEL, belimumab
CNI, calcineurin inhibitor
CYC, cyclophosphamide
eGFR, estimated glomerular filtration rate
GC, glucocorticoids
HCQ, hydroxychloroquine
IV, intravenous
MMF, mycophenolate mofetil
MP, methylprednisolone
PO, per os
RTX, rituximab
SGLT2i, sodium-glucose transporter, two inhibitors
TAC, tacrolimus
Upr, urine protein
VKA, vitamin K antagonists
VOC, ciclosporin

SLE CPG Summary

In diagnosing SLE patients, there are three algorithms that the clinician can follow accurately and derive an accurate classification using the EULAR Systematic Lupus Collaborating Clinics (SLICC) criteria 2019, which replaces the SLICC criteria of 1997 and 2012. Firstly, there is an ANA positive titer with an SLICC score of 10 or more, an ANA titer positive with an SLICC score of less than 10, and an ANA titer adverse pathway for which clinical domains and immunological domains are met, which classifies the patient with clinical SLE. The clinicians must remember that 20% of the patients will test negative or have false negative ANA titers while still clinically suffering from SLE; hence, the clinician must consider alternative criteria and nonclinical features of Lupus such as myocarditis, fatigue syndrome, Raynaud's syndrome, SICCA, Mouth sore in pemphigus vulgaris, and other atypical rashes.