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

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Objective. To provide evidence-based and expert guidance for the treatment and management of non-renal systemic lupus erythematosus (SLE); treatment and management of lupus nephritis are addressed in a separate guideline.

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

Results. We present recommendations and ungraded, consensus-based good practice statements for the treatment and management of SLE that are applicable to pediatric and adult patients. Recommendations emphasize uniform treatment with hydroxychloroquine, limiting duration of glucocorticoid use, and early introduction of conventional and/or biologic immunosuppressive therapies to achieve and maintain control of SLE inflammation (remission or a low level of disease activity), reduce SLE-related morbidity and mortality, and minimize medication-related toxicities.

Conclusion. This guideline presents direction regarding treatment and management of SLE and provides a foundation for well-informed, shared clinician–patient decision-making. 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 person with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a clinically heterogeneous, multisystem autoimmune disease with a prevalence of 72.8/100,000 persons in the United States[1] and a predilection for reproductive-aged females; prognosis is worse for those of Black, Hispanic, American Indian/Alaskan Native, and Asian ancestry.[1–7] Genetic, epigenetic, hormonal, infectious, and environmental factors contribute to its pathogenesis. Guidelines for management of SLE in adults were last published by the American College of Rheumatology in 1999.[8] Since then, treatment regimens incorporating mycophenolate mofetil/mycophenolic acid or lower-dose cyclophosphamide (CYC) have proven effective compared to the older, higher-dose CYC regimen. Belimumab, voclosporin, and anifrolumab are US Food and Drug Administration (FDA)-approved for SLE and/or lupus nephritis (LN) treatment, and clinical trials are ongoing to identify additional new therapies. This guideline addresses overall treatment strategies as well as management of specific organ system manifestations, except for LN which is covered in a separate guideline.[9]

These recommendations follow general guiding principles (Table 1) and are based on systematic literature review, patient values and preferences, and clinical expertise of a heterogenous guideline panel, including 31 adult rheumatologists, 5 pediatric rheumatologists, 2 dermatologists, 1 pediatric dermatologist, 1 rheumatology physician assistant, and 2 people with SLE.

Recommendations are intended to promote optimal outcomes for common SLE scenarios using therapies available in the United States as of 2024 and are applicable to the pediatric population with specific considerations, as noted. In practice, therapeutic decisions will vary based on clinical presentation, patient preferences, and limitations in access to specialists, procedures, and medications.

METHODS

This guideline follows the American College of Rheumatology (ACR) guideline development process using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology[10,11] and ACR policy that guides the management of conflicts of interest and disclosures.[12] Supplementary Materials 1 includes a detailed description of the methods. The Core Leadership Team (LRS, RAM, AA, BLB, MD, AD, LTH, MBS, VPW) drafted clinical population, intervention, comparator, and outcomes (PICO) questions (see 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 the evidence report (see Supplementary Materials 3). Moderated by three rheumatologists (SG, LTH, MBS), a Patient Panel of 13 individuals with SLE and varied organ system manifestations provided their perspectives on therapy and management; a separate manuscript detailing the Patient Panel process, discussion, and results is in progress. Tw-

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SIGNIFICANCE

- Hydroxychloroquine should be standard therapy for all people with SLE unless contraindicated.
- Glucocorticoids should be used primarily for initial control of immune-mediated inflammation and during flares as needed, with tapering as soon as possible.
- Early introduction of immunosuppressive therapies (conventional and/or biologic) for ongoing SLE activity is encouraged to achieve control of SLE inflammation (remission or a low level of disease activity), reduction in SLE-related morbidity and mortality, and minimization of glucocorticoid-related toxicities.

o Patient Panel members served as Voting Panel members and shared the Patient Panel's concerns and preferences. The Voting Panel reviewed evidence and voted on recommendations derived from the initial PICO questions; certain recommendations were rewritten and revoted upon based on Voting Panel discussion. Per ACR policy, consensus required ≥70% agreement on both direction (for or against) and strength (strong or conditional) of each recommendation. A recommendation is categorized as strong if the panel was very confident that the benefits of the intervention clearly outweighed its harms, or vice versa. A conditional recommendation denotes uncertainty regarding the balance of benefits and harm due to low-quality evidence, or that the decision is particularly sensitive to individual patient preferences or cost constraints. Good practice statements (GPS) were also generated; these are actionable statements where the desirable effects clearly outweigh the undesirable effects of an intervention.[13] 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. This guideline will be reviewed and updated periodically.

Table 1. Guiding Principles*

The goals of SLE treatment are to achieve and maintain SLE remission or low lupus disease activity, reduce SLE-related morbidity and mortality, and minimize treatment related toxicities.
Collaborative care between rheumatologists and appropriate specialists should be provided whenever possible.
Shared decision-making is essential to respect patient values and preferences and leads to better treatment adherence and outcomes.
Healthcare disparities, including racialized and socioeconomic disparities, are crucial factors impacting outcomes of those living with SLE; treatment recommendations are aimed to alleviate health disparities.
Pediatric-specific guidance is provided when possible.
Some therapies are presented without hierarchy when evidence-based data, clinical expertise, and patient-reported experiences do not clearly support the use of one medication over another; treatment decisions should be individualized to the patient's clinical status and preference.
Potential limitations to implementing care recommendations may arise due to limitations in access to testing, specialists, procedures, and medications; if recommended therapies are unavailable, are not tolerated, or are not preferred by patients, we encourage discussion of reasonable alternative therapies.
Assumptions • All treatment recommendations assume other appropriate workups have been done to rule out non-SLE etiologies. • Organ-specific treatment recommendations assume all patients are taking hydroxychloroquine unless there is a contraindication to therapy.

* SLE, systemic lupus erythematosus.

Scope

Treatment for all people with SLE regardless of age, ancestry, or other individual patient variables is presented here. General and organ-specific treatment recommendations and monitoring are offered, except for LN, which is addressed in a separate guideline.[9] Some SLE-related clinical issues were beyond the scope of this project. We do not offer guidance on diagnosis of SLE and do not include recommendations for treatment of certain broader and/or less well understood SLE-related issues including "type 2" SLE symptoms, mental health issues, and antiphospholipid syndrome (APS).

"Type 2" SLE symptoms, including fatigue, generalized pain, and brain fog, impact quality of life for individuals with SLE[14]. The pathophysiology and optimal treatment of "type 2" symptoms are incompletely understood and are acknowledged as a high research priority; treatment recommendations here address SLE manifestations that are more clearly mediated through inflammation ("type 1"). Similarly, depression and anxiety – common in adults, adolescents, and children with SLE – often impact general well-being for people with SLE.[15,16] No specific recommendations are offered, but we suggest that routine mood screening and attention to mental health should ideally be incorporated into general SLE care, with appropriate referrals to specialists when indicated. Presence of antiphospholipid antibodies (aPL) impacts therapy considerations for patients with SLE. This guideline does not include specific recommendations for APS; while often overlapping with SLE, therapy and management of APS are beyond the scope of this SLE treatment guideline.

Comprehensive management recommendations for common SLE-associated comorbidities are also considered beyond the scope of this project, but important adjunct considerations referencing other guidelines and sources are briefly summarized as a resource to complement the SLE-directed treatment recommendations. Recommendations regarding SLE treatment options during pregnancy are not included; they are addressed in the ACR's guideline for the management of reproductive health in rheumatic and musculoskeletal diseases.[17]

RESULTS/RECOMMENDATIONS

Terminology, definitions, and abbreviations are summarized in Table 2; recommendations and GPS are listed in Table 3. Limitations in available evidence and heterogeneity in clinical practice patterns

Table 2. Terminology, definitions and abbreviations*

Terminology	ACR SLE Treatment Guideline Definition
SLE Disease Activity Level	
Severe	Very active disease that may be organ- and/or life-threatening or cause permanent damage or severe symptoms due to active inflammation
Moderate	Active, uncontrolled disease that is not immediately life-threatening and/or causes moderate symptoms due to active inflammation
Mild	Active disease that is not immediately organ- or life-threatening and/or causes no more than mild symptoms due to active inflammation
SLE Disease Activity State	
Remission	Symptoms and signs of disease activity are significantly reduced or absent for an extended time. Specific definitions vary. Example: DORIS remission: SLEDAI-2K = 0, Prednisone ≤5 mg/day, PGA <0.5, stable antimalarials, immunosuppressives, biologics (no requirement for normal serology)[34]
Low level disease activity	A period with a low level of disease activity with no major organ involvement. Specific definitions vary. Example: Lupus Low Disease Activity State (LLDAS): SLEDAI-2K score ≤4 (with no activity in major organ systems or new/worsening symptoms), prednisone ≤7.5 mg/d, PGA ≤1, stable antimalarials, immunosuppressives, biologics[28]
Medication Abbreviations	
Anti-CD20-therapy	Rituximab, obinutuzumab
AZA	Azathioprine
Biologic Immunosuppressive therapy	IL-1 inhibitor, anti-CD 20 therapy, anifrolumab, belimumab
CCB	Calcium-channel blocker
CNI	Calcineurin inhibitor
CYC	Cyclophosphamide [monthly IV CYC, 0.5-1.0 g/m2]
Conventional Immunosuppressive therapy	Azathioprine, calcineurin inhibitors, intravenous cyclophosphamide, mycophenolic acid analogs, methotrexate
GC	Glucocorticoid
GPS	Good practice statement
HCQ	Hydroxychloroquine
Immunosuppressive therapy	Conventional and biologic therapies
IVIG	Intravenous immunoglobulin G
MPAA	Mycophenolic acid analogs (including mycophenolate mofetil [MMF] and mycophenolic acid [MPA])
MTX	Methotrexate
PLEX	Plasma exchange

* Terminology, definitions, and abbreviations 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. ACR, American College of Rheumatology; IL, interleukin; PGA, Physician Global Assessment; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

among Voting Panel members presented important challenges in reaching consensus on many recommendations. Explanatory text throughout the "Results" section addresses this, as well as the rationale and suggested implementation of the recommendations.

Monitoring SLE

In people with SLE, we conditionally recommend assessing disease activity regularly, including when there is a change in clinical status or SLE-directed medications

Evidence was indirect and extrapolated from data showing that having a low level of disease activity is associated with better long-term outcomes.[18,19] The frequency of disease activity assessment was discussed extensively; no agreement was reached regarding any one specific time interval leading to the decision to suggest that assessment be done regularly. The Voting Panel felt that while this will most often mean assessment at each follow-up visit, this acknowledges that timing will vary according to the type, severity, and rate of progression of SLE clinical manifestations. The Voting Panel prefers using a version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[20] to measure disease activity, conceding the challenge of administration in daily practice e.g., limitations in electronic medical record (EMR) infrastructure, provider burden, and time constraints. A physician's global assessment is also acceptable. The Voting Panel acknowledges the importance of information provided through patient-reported outcome tools as suggested by the ACR.[21]

In people with SLE, we conditionally recommend assessing disease damage at least annually

Damage accrual is associated with increased mortality.[22,23] Damage assessment involves tools such as the Systemic Lupus International Collaborating Clinics ACR Damage Index (SLICC/ACR-DI)[22] that evaluate long-term effects of both disease and

Table 3. Recommendations and Good Practice Statements*

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICO No.
Note: We suggest referring to the explanatory text throughout the "Results" section for each statement below, for details regarding rationale, development, and implementation of the recommendations and good practice statements.			
Monitoring			
In people with SLE, we conditionally recommend:			
Assessing disease activity regularly, including when there is a change in clinical status or SLE-directed medications.	Conditional	Very Low	P26a
Assessing disease damage at least annually.	Conditional	Very Low	P26b
Comorbidities and Risk Management			
GPS: *All people with SLE should receive screening, monitoring, and management for comorbid conditions associated with SLE and its therapies (including infection, cardiovascular disease, bone and joint damage, malignancy, reproductive health complications, and presence of antiphospholipid antibodies. (*Table 4*).*			
Medication Guidance and Treatment Goals			
GPS: *The goal of SLE treatment should be optimal control of disease (e.g., remission or a low level of disease activity) to improve long-term clinical outcomes.*			
GPS: *Prescribe glucocorticoids promptly to obtain rapid control of acute inflammation using the lowest dose and shortest duration necessary and initiate immunosuppressive therapy early to minimize glucocorticoid-related toxicity.*			
Glucocorticoid therapy:			
In people with SLE: With organ- or life-threatening SLE flares: ...We conditionally recommend pulse methylprednisolone treatment (250–1,000 mg for 1–3 days) followed by oral glucocorticoid taper over high-dose oral glucocorticoid taper without pulse treatment.	Conditional	Very low	P29.1
With stable controlled SLE on prednisone >5 mg/day: ...We strongly recommend tapering the prednisone to a dose of ≤5 mg daily (and ideally to zero) within 6 months.	Strong	Low	P28.1
With sustained remission on prednisone ≤5 mg/day: ...We conditionally recommend a slow taper toward zero.	Conditional	Very low	P32.1
Who are unable to taper prednisone to ≤5 mg/day: ...We conditionally recommend initiating or escalating immunosuppressive therapy.	Conditional	Very low	P30.1, P31.1
Hydroxychloroquine therapy: In people with SLE, we strongly recommend routine treatment with HCQ unless contraindicated.	Strong	Very low to Moderate	P35.1
In people with SLE, we conditionally recommend continuing HCQ therapy indefinitely, even in the setting of sustained remission.	Conditional	Low	P36.3, P36.4
In people with SLE receiving HCQ therapy: ...We conditionally recommend a long-term average daily HCQ dose goal of ≤5 mg/kg over a dose goal of >5 mg/kg to minimize retinal toxicity; use of short courses of higher dose (between 5 and 6.5 mg/kg/d) therapy may be necessary at initiation of treatment or to maintain disease control.	Conditional	Very low to Low	P33.1
Immunosuppressive therapy: In people with SLE with sustained clinical remission or low disease activity: ...We conditionally recommend tapering immunosuppressive therapy after 3-5 years with the goal of discontinuation.	Conditional	Low	P36.1, P36.2
General treatment strategies			
GPS: *People with active SLE symptoms should be diagnosed and treated promptly, with severity of lupus activity guiding intensity and choice of therapy.*			
GPS: *When multiple organ systems are involved at onset or during a flare of SLE, therapy should be directed toward all manifestations but should prioritize areas at greatest risk for irreversible damage.*			
GPS: *Organ- or life-threatening SLE should be treated urgently/emergently with aggressive therapy (e.g., pulse/high-dose glucocorticoid and immunosuppressive therapy), including consideration of combination therapies, as time may not permit sequential therapy; the clinical situation and patient's preference should guide the specific combination therapy.*			
GPS: *When medications, procedures, and surgeries beyond the scope of rheumatology practice are considered, the decision to proceed with such therapies requires multidisciplinary discussion between the rheumatologist and the relevant specialists/proceduralists/surgeons.*			
GPS: *When clinical or serologic findings suggest an additional diagnosis or overlap with SLE (e.g., aquaporin-4 antibodies in setting of known SLE and new onset transverse myelitis or optic neuritis), therapy should be adjusted if necessary, depending upon which process is predominant and in consultation with the relevant specialist(s).*			
Organ-specific manifestations*			
For ongoing SLE disease activity in any organ system(s) refractory to initial therapy,			

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICO No.
...We strongly recommend escalation of therapy.	Strong	Very low to Moderate	P37.1-P65.1
Hematologic			
Leukopenia: For asymptomatic neutropenia and/or lymphopenia (absolute counts <1,000/mcL for either) attributed to SLE ...We conditionally recommend *against* initiating immunosuppressive treatment (glucocorticoids, conventional or biologic immunosuppressants) in the absence of other lupus disease activity.	Conditional Against	Very Low	P37.1-3
Thrombocytopenia: For chronic asymptomatic thrombocytopenia (<30,000/mcL) attributed to SLE ...We conditionally recommend initiation of glucocorticoid with an additional therapy (MPAA, AZA, CNI, anti-CD 20 agents, belimumab and/or IVIG) over observation or glucocorticoid monotherapy.	Conditional	Very Low	P38.1-5
Thrombocytopenia: For symptomatic thrombocytopenia (i.e., active significant bleeding) attributed to SLE: ...We conditionally recommend initial glucocorticoid therapy with addition of IVIG and/or anti-CD20 therapy over the addition of conventional immunosuppressive agents.	Conditional	Very Low	P39.1-8
***Hemolytic Anemia*:** For symptomatic autoimmune hemolytic anemia (i.e., ischemic manifestations and/or hemodynamic instability) attributed to SLE: ...We conditionally recommend initial glucocorticoid therapy with addition of IVIG and/or anti-CD20 therapy over the addition of conventional immunosuppressive agents.	Conditional	Very Low	P40.1-8
Neuropsychiatric			
Severe neuropsychiatric syndromes: For Active lupus optic neuritis -OR- Lupus acute confusional state -OR- Active lupus mononeuritis multiplex: ...We conditionally recommend initial therapy with pulse/high-dose glucocorticoid taper plus immunosuppressive therapy with IV CYC, MPAA, or anti-CD20 therapy over pulse/high-dose glucocorticoid monotherapy alone.	Conditional	Very Low	P42.1-4 P44.1-4 P46.1-3
For active lupus myelitis: ...We conditionally recommend initial therapy with pulse/high-dose glucocorticoid and IV CYC over pulse/high-dose glucocorticoid combined with other (non-CYC) immunosuppressive agents.	Conditional	Very Low	P41.1-4
For active lupus psychosis: ...We conditionally recommend anti-psychotic therapy plus glucocorticoid, IV CYC, MPAA, or anti-CD20 therapy over anti-psychotic therapy alone.	Conditional	Very Low	P45.1
***Seizure**:* For seizures attributed to active SLE: ...We conditionally recommend anti-seizure medication plus glucocorticoid, CYC, MPAA, AZA, and/or anti-CD20 over anti-seizure medication alone.	Conditional	Very Low	P43.1, P43.2
***Cognitive dysfunction**:* For isolated cognitive dysfunction attributed to SLE and documented by neuropsychological testing: ...We conditionally recommend *against* adding immunosuppressive therapy (including glucocorticoid) to cognitive therapy over using cognitive therapy alone.	Conditional Against	Very Low	P48.1, P48.2
Cutaneous/mucocutaneous			
GPS: *People with SLE should be educated on the use of sunscreen and other sun-protection measures to reduce risk of rash and potential disease flare.*			
GPS: *Initial therapy for cutaneous lupus rash—in addition to HCQ—should be topical, including glucocorticoid and/or calcineurin inhibitors (*Table 6*); initial therapy may also include a course of intralesional glucocorticoid with dermatology and/or a brief, limited course of oral glucocorticoid.*			
Acute, subacute and chronic cutaneous lupus: For mild, ongoing skin-predominant lupus despite treatment with HCQ and/or topical therapies: ...We conditionally recommend modifying antimalarial therapy (adding quinacrine or switching to chloroquine) over adding an immunosuppressive agent.	Conditional	Very low	P50.1, P50.2 P51.1, P51.2

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICO No.
For ongoing moderate-severe cutaneous lupus refractory to topical and antimalarial therapies, and/or oral glucocorticoid necessitating escalation of therapy ...We conditionally recommend the addition of MTX, MPAA, anifrolumab, and/or belimumab.	Conditional	Very low to Moderate	P50.3 P51.5, P51.7
For ongoing moderate-severe cutaneous lupus refractory to topical therapies, antimalarials, and conventional and/or biologic immunosuppressive agents necessitating escalation of therapy: ...We conditionally recommend adding or substituting lenalidomide.	Conditional	Very low	P51.6
Bullous lupus erythematosus:			
For mild ongoing bullous lupus despite treatment with topical therapies and antimalarial therapies: ...We conditionally recommend the initial addition of dapsone over initiation of glucocorticoid.	Conditional	Very low	P52.1
For moderate-severe bullous lupus refractory to topical therapies, antimalarials, and/or oral glucocorticoid necessitating escalation of therapy: ...We conditionally recommend adding a conventional immunosuppressive agent (MPAA, MTX, AZA) and/or anti-CD-20 therapy.	Conditional	Very low	P52.2, P52.3
Chilblain lupus:			
For chilblain lupus despite symptomatic, topical, and antimalarial therapies (including quinacrine): ...We conditionally recommend the addition of pentoxifylline, PDE5 inhibitors (e.g., sildenafil, tadalafil) and/or calcium channel blockers (e.g., nifedipine) over initiation of immunosuppressive therapies.	Conditional	Very low	P53.1-P53.5
Leukocytoclastic vasculitis:			
For ongoing mild cutaneous vasculitis despite topical and antimalarial therapies: ...We conditionally recommend addition of dapsone or colchicine over immunosuppressive therapies including oral glucocorticoid.	Conditional	Very low	P54.4, P54.5
Serositis			
Pleuropericarditis:			
For lupus pleuropericarditis: ...We conditionally recommend initial treatment with NSAID, colchicine, or their combination, with a low threshold for escalation to glucocorticoid therapy over initiating glucocorticoid therapy alone.	Conditional	Very low	P57.1, P58.2
For ongoing/recurrent episodes of lupus pleuropericarditis despite treatment with HCQ, NSAIDs, colchicine, and/or glucocorticoids necessitating escalation of therapy: ...We **conditionally** recommend conventional (MPAA, AZA) or biologic immunosuppressive therapies.	Conditional	Very low	P58.3 P58.4
Musculoskeletal			
GPS: *Initial therapy for acute or recurrent episodes of inflammatory arthritis in people with SLE may include a course of NSAID or a limited course of oral glucocorticoid while waiting for recommended long-term therapies to take effect.*			
Arthritis:			
For persistent or recurrent active SLE arthritis on HCQ, regardless of prior/current NSAIDs or short-term glucocorticoid therapy: ...We conditionally recommend initial therapy with MTX, MPAA, or AZA, with a low threshold to add or substitute with belimumab or anifrolumab for inadequate response over initial biologic therapy.	Conditional	Very low to Low	P60.1-5 P61.1-5
Systemic Vasculitis			
For vasculitis attributed to active SLE: ...We conditionally recommend initial therapy with pulse/high-dose glucocorticoid taper and conventional (IV CYC, MPAA, AZA) or biologic (anti-CD 20 therapy, belimumab, anifrolumab) immunosuppressive therapy over glucocorticoid monotherapy alone.	Conditional	Very low to Low	P63.1-3
For severe vasculitis attributed to SLE: ...We conditionally recommend IV CYC or anti-CD20 therapy as initial therapy over other immunosuppressive therapies.	Conditional	Very low	P63.2, P63.3

(Continued)

Table 3. (*Cont'd*)

Recommendations and Good Practice Statements	Strength	Level of Evidence	PICO No.
For life-threatening vasculitis attributed to active SLE (e.g., diffuse alveolar hemorrhage or mesenteric vasculitis): ...We conditionally recommend the addition of PLEX and/or IVIG to pulse/high-dose glucocorticoid taper and immunosuppressive therapy over glucocorticoid and immunosuppressive therapy alone.	Conditional	Very low	P63.4
Cardiopulmonary			
Myocarditis: For lupus myocarditis that is acute and/or worsening: ...We conditionally recommend treatment with glucocorticoid and IV CYC, MPAA, anti-CD20 therapy, and/or IVIG over glucocorticoid monotherapy.	Conditional	Very low	P64.1
Non-bacterial (Libman-Sacks) endocarditis: For non-bacterial (Libman-Sacks) endocarditis: ...We conditionally recommend immunosuppressive therapy and/or anticoagulation.	Conditional	Very low	P65.1

* Treatment and management of lupus nephritis is addressed in the 2024 American College of Rheumatology Guideline for the Screening, Treatment, and Management of Lupus Nephritis.[9] AZA, azathioprine; CNI, calcineurin inhibitor; CYC, cyclophosphamide; GPS, good practice statement; HCQ, hydroxychloroquine; IVIG, intravenous Ig; MTX, methotrexate; MPAA, mycophenolic acid analogs; NSAID, non-steroidal anti-inflammatory drugs; PDE5, phosphodiesterase type 5; PICO, population, intervention, comparator, and outcome; PLEX, plasma exchange; SLE, systemic lupus erythematosus.

medication toxicities. The process of formally assessing damage criteria can serve to identify individual vulnerabilities and prompt changes in therapy or management; it can also guide discussion of prognosis. Yearly evaluation is favored, especially for pediatric/adolescent patients who are undergoing rapid physical development.[24]

Comorbidities and Risk Management

GPS: All people with SLE should receive appropriate screening, monitoring, and management for comorbid conditions associated with SLE and its therapies

SLE and its therapies are associated with infection, cardiovascular disease, bone and joint damage (e.g., osteoporosis, avascular necrosis), malignancy, and reproductive health complications. aPL may increase risk for certain disease manifestations and disease damage;[25] accordingly, aPL assessment should be included in comorbidity screening. Promoting a healthy diet, sleep hygiene, and physical activity for people with SLE is important. Reduced comorbidity risk and improved management are ideally achieved by collaboration with primary care providers and relevant subspecialists. We do not provide formal recommendations addressing comorbidities due to scope limitations but do include a summary of general suggestions with relevant references in Table 4. We emphasize that these suggestions are based on outside sources: they are not formal recommendations. Table 4 is included to provide convenient access to relevant information for the clinician, and as a reminder to incorporate comorbidity management into general SLE care.

Medication Guidance and Treatment Goals

Glucocorticoids, antimalarials, and conventional and biologic immunosuppressive therapies are the cornerstones of treatment for people with SLE, aimed at reducing disease activity while limiting treatment toxicity (Figure 1). Adherence to antimalarial therapy should be assessed when any change in medication use is anticipated. Table 5 reviews monitoring and dosing for commonly used SLE medications. Table 5 presents supporting information that is relevant to but not part of our formal recommendations with the goal of providing convenient access to these published suggestions from outside sources. Prescribing and monitoring should be tailored to individual clinical situations.

GPS: Treatment for SLE should be directed toward optimal control of disease (remission or low level of disease activity) in order to improve long-term clinical outcomes

Prolonged medication-free remission is rare in SLE;[26] however, remission or low disease activity on stable antimalarial and immunosuppressive therapies with low-dose (or no) glucocorticoid are often attainable. Routine implementation of a treat-to-target (T2T) strategy is an important future goal for SLE management.[27–32] T2T involves a formal process of ongoing treatment adjustments to attain a well-defined, clinically meaningful goal, and has been recommended by the ACR for

Table 4. Suggestions for adjunctive therapies and management of comorbidities*

Suggested Comorbidity Guidance and Management	
General	
Lifestyle[a,b]	Physical activity, sleep hygiene, and therapeutic exercise Photoprotection Smoking cessation Psychosocial interventions
a. EULAR recommendations for the non-pharmacological management of systemic lupus erythematosus and systemic sclerosis. Parodis I, et al. Ann Rheum Dis 2024;83:720.	
b. Recommendations for physical activity and exercise in persons living with Systemic Lupus Erythematosus (SLE): consensus by an international task force. Blaess J, et al. RMD Open 2024;10:e004171.	
Cardiovascular Health	
ASCVD risk:	SLE is a "risk-enhancing factor": Assess using risk calculator and manage traditional risk factors[c,d];
c. ***2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines****. Arnett DK, et al. J Am College Cardiol. 2019;74:1376.*	
d. ***The use of risk-enhancing factors to personalize ASCVD risk assessment: evidence and recommendations from the 2018 AHA/ACC multi-society cholesterol guidelines****. Agarwala A, et al. Curr Cardio Risk Rep 2019;13:1.*	
Infection Screening	
HBV	General: All adults at least once in lifetime[e] All people with SLE before immunosuppressive therapy (including glucocorticoid according to dose/duration)[f]
HCV	General: All adults at least once in lifetime (except where HCV prevalence is <0.1%)[e] Consider for all people with SLE before immunosuppressive therapy (including glucocorticoid according to dose/duration)[f]
Tuberculosis	Adults: Before biologic (and targeted synthetic) immunosuppressives[g]; Consider before conventional immunosuppressives, other immunosuppressives and/or glucocorticoids (according to dose/duration)[f] Children and adolescents: Before biologic immunosuppressives[h]
HIV	Adults: Before biologic immunosuppressives[f] Consider before conventional (and targeted synthetic) immunosuppressives, other immunosuppressives and/or glucocorticoids (according to dose/duration)[f]
e. ***Centers for Disease Control and Prevention***	
f. ***2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases.*** *Fragoulis GE, et al. Ann Rheum Dis 2023;82:742–753.*	
g. ***United States Preventive Services Taskforce***	
h. ***American Academy of Pediatrics***	
Vaccinations	
High-dose influenza, Pneumococcal, Recombinant VZV	>18 years of age on immunosuppressive therapy[i]
COVID-19	All ages ≥6 months if moderately/severely immunocompromised (initial and boosters)[e]
RSV	Adults 60–74 years if increased risk; includes immunocompromised individuals[e]
HBV	Adults 19–59 years[e] Adults ≥60 years with risk factors Children/adolescents <19 years
HPV	Adults >26 years and <45 years on immunosuppressive therapy (if not previously vaccinated)[i] All children/adolescents/young adults (9–26 years)[e]
e. ***Centers for Disease Control and Prevention***	
i. ***2022 American College of Rheumatology guideline for vaccinations in patients with rheumatic and musculoskeletal diseases.*** *Bass AR, et al. Arthritis Care Res (Hoboken) 2023;75:449–464.*	
Infection Prophylaxis	
PJP	Consider for all people on high-dose glucocorticoid (daily dose >15–30mg of prednisolone or equivalent for >2–4 weeks[f]) Note: Prophylaxis considered controversial outside of organ transplant[j]; rates in people with SLE are very low (0.4%)[k] Higher risk: • Glucocorticoid in combination with immunosuppressives[f] • Underlying interstitial lung disease[f] • Lymphopenia <500[f]
HBV[l]	Determine by both hepatitis B serologic profile and immunosuppressive regimen[9] *Serologic profiles*:

(Continued)

Table 4. (*Cont'd*)

Suggested Comorbidity Guidance and Management	
	• Higher risk: HBsAg positive and anti-HBc positive. • Lower risk: HBsAg negative and anti-HBc positive *Immunosuppressive regimens:* Prophylaxis for high reactivation risk therapy (>10%) including treatment with: • B-cell depleting therapy • Moderate- to high-dose glucocorticoid (>20 mg daily for > 4 weeks) Consider prophylaxis for moderate reactivation risk therapy (1–10%) including treatment with: • TNF-inhibitors • Other cytokine inhibitors Monitor only for low reactivation risk therapy (<1%) including treatment with: • Conventional immunosuppressives
f. ***2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases.*** *Fragoulis GE, et al. Ann Rheum Dis 2023;82:742–753.*	
j. ***Risk factors and prevention of Pneumocystis jirovecii pneumonia in patients with autoimmune and inflammatory diseases****. Ghembaza A, et al. Chest 2020;158:2323–2332.*	
k. ***Rates of Pneumocystis jirovecii pneumonia and prophylaxis prescribing patterns in a large electronic health record cohort of patients with systemic lupus erythematosus****. Boone B, et al. Sem Arthritis Rheum 2022;57:152106.*	
l. ***American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy****. Perrillo RP, et al. Gastroenterology 2015;148:221–244.e3.*	
Bone health	
No chronic GC [g]	Screen all women 65 years and older Screen postmenopausal women <65 years at risk No recommendations for men
GC ≥2.5 mg pred > 3 mo [m]	
Screening	≥40 years: FRAX and BMD with vertebral fracture assessment or spinal x-rays <40 years: BMD with vertebral fracture assessment or spinal x-rays
Therapy	Assess fracture risk as per ACR guideline Offer oral bisphosphonates (or alternative) to all with medium or higher fracture risk. For very high risk, consider denosumab or parathyroid hormone/ parathyroid hormone-related protein over bisphosphonates.
g. **United States Preventive Services Taskforce**	
m. ***2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis****. Humphrey MB, et al. Arthritis Rheumatol 2023;75:2088–2102.*	
Cancer screening	
General [n,o]	All general population screening measures should be observed Consider urine cytology screening if prior CYC therapy
Cervical cancer [p,q]	Enhanced screening protocol: All women with SLE, regardless of immunosuppressive use, should follow screening guidelines for HIV-infected women[p]
n. ***European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies.*** *Mosca M, et al. Ann Rheum Dis 2010;69:1269–1274.*	
o. ***Managing cancer risk in patients with systemic lupus erythematous****. Ladouceur A, et al. Expert Rev Clin Immunol 2018;14:793–802.*	
p. ***Guidelines for cervical cancer screening in immunosuppressed women without HIV infection****. Moscicki AB, et al. J Low Genit Tract Dis 2019;23:87–101.*	
q. ***New WHO recommendations on screening and treatment to prevent cervical cancer among women living with HIV: policy brief****. World Health Organization; 2021.*	
Reproductive health	
Contraception [r]	IUD or subdermal progestin implant preferred No estrogen-containing methods if active disease or aPL-positive IUD or 2 methods if taking MPAA
Fertility [r]	Defer assisted reproductive therapy if active SLE Low molecular weight heparin for ovarian stimulation in aPL+ patients Fertility preservation with monthly IV CYC: • Females: Gonadotropin-releasing hormone agonist co-therapy • Males: consider pre-treatment sperm cryopreservation
Pregnancy [r]	Defer pregnancy if active SLE Avoid pregnancy if significant organ damage Attempt conception after stable/low disease activity on pregnancy compatible-medications for 4–6 months Low-dose aspirin for preeclampsia prophylaxis Hydroxychloroquine (if not contraindicated) Assess, monitor, and treat for aPL and anti-Ro/La antibodies

(Continued)

Table 4. (*Cont'd*)

Suggested Comorbidity Guidance and Management	
Menopause[r]	Avoid hormone replacement therapy if active SLE or aPL-positive
r. ***2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases.*** *Sammaritano LR, et al. Arthritis Rheumatol 2020;72:529–556.*	
Medication toxicity	
Glucocorticoid	Assess for glucocorticoid withdrawal syndrome and adrenal insufficiency with taper which may mimic nonspecific SLE symptoms[s]
s. ***European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and therapy of glucocorticoid-induced adrenal insufficiency.*** *Beuschlein F, et al. Eur J Endocrinol 2024;190:G25–G51.*	

* This table is a synthesis of published sources, some with limited data and/or differing recommendations, and was constructed with input from SLE Guideline Team members. We present suggestions (with reference to outside sources) to guide screening and management of common comorbidities. These are suggestions only; they are not formal recommendations. Care for individuals with SLE will vary based on their clinical situation and personal preferences. References and guidelines cited here are the most current sources available at the time of guideline preparation and will be updated when this guideline is revised; however, be aware that revisions of these sources may be published in the interim.
The vaccine summary here includes recommendations for immunizations deemed relevant to SLE and is not comprehensive. Children and adolescents with cSLE are more likely to have delays in their vaccine schedule due to immunosuppressive medications; consult the CDC website for recommendations: https://www.cdc.gov/vaccines/?CDC_AAref_Val=https://www.cdc.gov/vaccines/schedules/hcp/schedule-changes.html#guidance.
ACC, American College of Cardiology; ACR, American College of Rheumatology; AHA, American Heart Association; aPL, antiphospholipid antibodies; ASCVD, atherosclerotic cardiovascular disease; BMD, bone mineral density; cSLE, childhood-onset SLE; CYC, cyclophosphamide; FRAX, fracture risk assessment tool; GC, glucocorticoid; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; IV, intravenous; IUD, intrauterine device; MPAA, mycophenolic acid analogs; PJP, *Pneumocystis jirovecii* pneumonia; RSV, respiratory syncytial virus; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; VZV, varicella zoster virus.

treatment of rheumatoid arthritis.[33] DORIS remission and the Lupus Low Disease Activity State (LLDAS)[28,34] definitions (Table 2) are the most widely accepted validated clinical goals for SLE, however, evidence from randomized trials of T2T for SLE are not yet available. SLE disease modification, i.e., slowing or preventing organ damage, remains an emerging concept.[30,31,35]

Glucocorticoid Therapy

GPS: Prescribe glucocorticoids promptly to obtain rapid control of inflammation using the lowest dose for the shortest duration and initiate immunosuppressive therapy early to minimize glucocorticoid-related toxicity

In people with organ- or life-threatening SLE flares, we conditionally recommend pulse methylprednisolone treatment (250 – 1,000 mg for 1-3 days) followed by oral glucocorticoid taper over high-dose oral glucocorticoid taper without pulse treatment

Glucocorticoids provide rapid suppression of SLE disease activity, but side effects may lead to significant toxicity.[36,37] Intravenous (IV) glucocorticoids have a more rapid onset of action than oral preparations and are preferred for life- or organ-threatening manifestations of SLE, such as transverse myelitis or severe thrombocytopenia; however, Voting Panel members acknowledged that challenges with access to infusion centers may limit their outpatient use.

In people with stable controlled SLE taking prednisone >5 mg/day we strongly recommend tapering the prednisone to a dose of ≤5 mg/day (and ideally discontinue prednisone) within 6 months

In people with sustained remission taking prednisone ≤5 mg/day, we conditionally recommend a slow taper toward prednisone discontinuation

In people unable to taper prednisone to ≤5 mg/day, we conditionally recommend initiating or escalating immunosuppressive therapy

Risks of glucocorticoid toxicity led to a strong recommendation to taper glucocorticoids quickly to avoid long-term exposure.[36,37] Tapering off glucocorticoids completely (with addition of immunosuppressive therapy when unable to do so) is recommended because even low-dose long term glucocorticoid confers risk.[38] The recommendation to taper off completely is conditional because the balance of benefit and harm will vary depending on individual risks as well as personal preferences.[39] For individuals with stable controlled disease we strongly discourage a chronic daily dose of >5 mg due to the well-recognized harms of chronic therapy. Even for those in clinical remission, (i.e., DORIS remission, which permits 5 mg/d prednisone), we encourage an effort to reduce or stop prednisone. A slow taper in 1 mg increments from a low prednisone dose such as 5 mg/day, with continued hydroxychloroquine (HCQ) or other therapies, may permit discontinuation.[40–42] Glucocorticoid withdrawal syndrome and adrenal insufficiency may be confused with nonspecific SLE symptoms and may impact the ability to taper off glucocorticoid therapy.[43]

Hydroxychloroquine therapy

In people with SLE, we strongly recommend routine treatment with HCQ unless contraindicated

In people with SLE, we conditionally recommend continuing HCQ therapy indefinitely, even in the setting of sustained remission

In people with SLE receiving HCQ therapy, we conditionally recommend a long-term average daily HCQ dose goal of ≤5 mg/kg over a dose goal of >5 mg/kg to minimize retinal toxicity; use of short courses of higher dose (between 5 and 6.5 mg/kg/d) therapy may be necessary at initiation of treatment or to maintain disease control

Hydroxychloroquine is preferred over other antimalarials due to its better safety profile,[44] although use of other antimalarials may be considered. Due to its multiple benefits, continuing HCQ with appropriate monitoring (Table 5) is strongly recommended, even during remission. Level of certainty for evidence varied from very low to moderate for differing outcomes; it was moderate for complete and partial response (Supplementary Materials 3). A maintenance goal of ≤5 mg/kg/day is endorsed to minimize long-term toxicity. Higher doses (between 5 and 6.5 mg/kg/day) may be justified for shorter term use, i.e., when initiating therapy, addressing periods of incomplete disease control, or during pregnancy.[45–48] Routine screening for HCQ retinopathy is important for all long-term HCQ users to mitigate the risk of vision loss, as it can identify asymptomatic, early-stage retinopathy.[47,49] The recommendation for indefinite use of HCQ is conditional; further research is needed to determine benefits versus harms. Given challenges in testing methodologies and interpretation, no consensus was reached on the optimal use of HCQ blood levels for guiding therapy. The primary utility of HCQ blood level monitoring presently lies in assessing adherence. As HCQ testing becomes more standardized and available, blood levels may inform medication dosing in the future.

Immunosuppressive Therapy

In people with SLE with sustained clinical remission or with low disease activity, we conditionally recommend tapering immunosuppressive therapy after 3-5 years, with the goal of discontinuation

The decision for discontinuation of immunosuppressive therapy should be based on individual risk for recurrence of active disease, severity of organ system involvement, and patient preference. Withdrawal of mycophenolate mofetil in individuals with quiescent SLE did not result in a higher rate of clinically significant disease reactivation in a randomized controlled trial.[50]

Pediatric considerations regarding medication guidance and treatment goals

This guideline is broadly applicable to childhood-onset SLE with specific considerations. A pediatric rheumatologist should be consulted, when possible, especially in highly complex or acutely ill patients. The combination of severe disease onset in youth necessitating high glucocorticoid exposure and its associated comorbidities can diminish peak bone mass, reduce adult height, and alter pubertal development.[51,52] Glucocorticoids impact physical appearance, influencing self-identity and mood.[53] Applying pediatric specific glucocorticoid dosing is important to minimize glucocorticoid adverse effects.[54] School attendance and performance should be assessed regularly for potential support with pharmacologic and non-pharmacologic intervention, as they can influence long-term vocational outcomes.[55] We recommend a planned transition to adult care to decrease risks of unscheduled health care utilization, care gaps, and disease flares.[51,52,56–59]

Organ-Specific Manifestations

Good practice statements and recommendations address both overall disease activity and specific organ system manifestations. For each organ system, GPS are listed first followed by recommendations.

GPS: People with active SLE symptoms should be treated promptly, with degree and type of lupus activity guiding intensity and choice of therapy

GPS: When multiple organ systems are involved at onset or during a flare of SLE, therapy should prioritize life-threatening systems or areas at greatest risk for irreversible damage

While it is important to identify optimal therapy for any given lupus manifestation, it is most common for multiple organ systems to be affected during a flare. For this reason, many of the good practice statements and recommendations in this guideline are general in scope and address broad tenets of multisystem therapy. Recommendations are provided to address organ specific manifestations where possible; these will be most useful when one organ system predominates. We suggest prioritizing life-threatening involvement and/or risk for irreversible damage when reconciling treatment recommendations that may have variable effectiveness for different organ systems in the setting of multi-organ involvement. We acknowledge, however, that this is a major challenge in management of SLE, and include this as a future research priority (Supplementary Materials 7).

GPS: Organ-or life-threatening SLE should be treated urgently/emergently with aggressive therapy (e.g., pulse/high-dose glucocorticoid and immunosuppressive therapy), including consideration of combination therapies, as time may not permit sequential therapy; the clinical situation and patient's preference should guide the specific combination therapy

GPS: When medications, procedures, and surgeries beyond the scope of rheumatology practice are considered, the decision to proceed requires multidisciplinary discussion between the rheumatologist and the relevant specialists/ proceduralists/surgeons

GPS: Adjust therapy when clinical or serologic findings suggest an additional diagnosis or overlap with SLE (e.g., aquaporin-4 antibodies in setting of known SLE and new onset transverse myelitis or optic neuritis), depending upon which process is predominant and in consultation with the relevant specialist(s)

For ongoing SLE disease activity in any organ system(s) refractory to initial therapy, we strongly recommend escalation of therapy over continuing the current therapy

The Voting Panel strongly recommends escalating treatment for ongoing, nonresponsive disease activity in any organ system. All members agreed upon the dual priorities of rapid and effective control of immune-mediated manifestations while minimizing glucocorticoid use. Organ-specific recommendations for specific therapies, however, are conditional for several reasons. Available evidence for organ-specific manifestations has lower certainty, with data stemming from observational studies or post-hoc analyses of randomized controlled trials. Studies often group manifestations differently: e.g., "severe neuropsychiatric lupus" includes myelitis, optic neuritis, and acute confusional state. Voting Panel participants' experience and clinical practice patterns varied. In the setting of limited evidence and an absence of data that directly compared treatment options for specific organ systems, Voting Panel members' clinical practice patterns and the preferences outlined by the Patient Panel guided recommendations. The initial PICO-generated recommendations were extensively discussed; when necessary, they were rewritten and revoted upon until consensus was reached. The final recommendations represent compromises among Voting Panel discussants who, while reviewing the same evidence, sometimes had varying clinical perspectives on optimal therapy.

In many clinical situations, the Voting Panel members did not recommend that one medication – or even one class of medication – take priority over another; however, in some clinical scenarios, a specific medication may be suggested when evidence and clinical experience is supportive. Recommendations may change in subsequent guideline revisions as more direct evidence becomes available.

HEMATOLOGIC MANIFESTATIONS

In situations with life-threatening hematologic manifestations, including marked cytopenias suggestive of macrophage activation syndrome or thrombotic microangiopathy[60], co-management with hematologists is suggested.

Leukopenia

For asymptomatic neutropenia and/or lymphopenia (absolute counts <1,000/mcL for either) attributed to SLE, we conditionally recommend *against* initiating immunosuppressive treatment (glucocorticoids, conventional or biologic immunosuppressants) in the absence of other lupus disease activity

Neutropenia attributed to SLE is treated with recombinant human granulocyte colony-stimulating factor (G-CSF) only if it is severe and associated with infection;[61] G-CSF should be used with caution as lupus flares have been reported after treatment.[62] Lymphopenia, which is more common than neutropenia, is usually associated with overall lupus disease activity and generally does not require specific treatment.[61]

Thrombocytopenia

For chronic asymptomatic thrombocytopenia (<30,000/mcL) attributed to SLE, we conditionally recommend initiation of glucocorticoid therapy with addition of mycophenolic acid analogs (MPAA), azathioprine (AZA), calcineurin inhibitor (CNI), anti-CD 20 agents, belimumab and/or IVIG over observation or glucocorticoid monotherapy alone

For symptomatic thrombocytopenia (i.e., active, significant bleeding) attributed to SLE, we conditionally recommend initiation of glucocorticoid therapy with IVIG and/or anti-CD20 therapy over the addition of conventional immunosuppressive agents

Most data are indirect and extrapolated from hematology guidance; the American Society of Hematology guideline suggests treatment rather than observation for platelet counts <30,000/mcL in cases of idiopathic thrombocytopenic purpura.[63,64] Initial aggressive treatment is generally followed by maintenance immunosuppressive therapy. The use of thrombopoietin mimetics is effective in SLE but

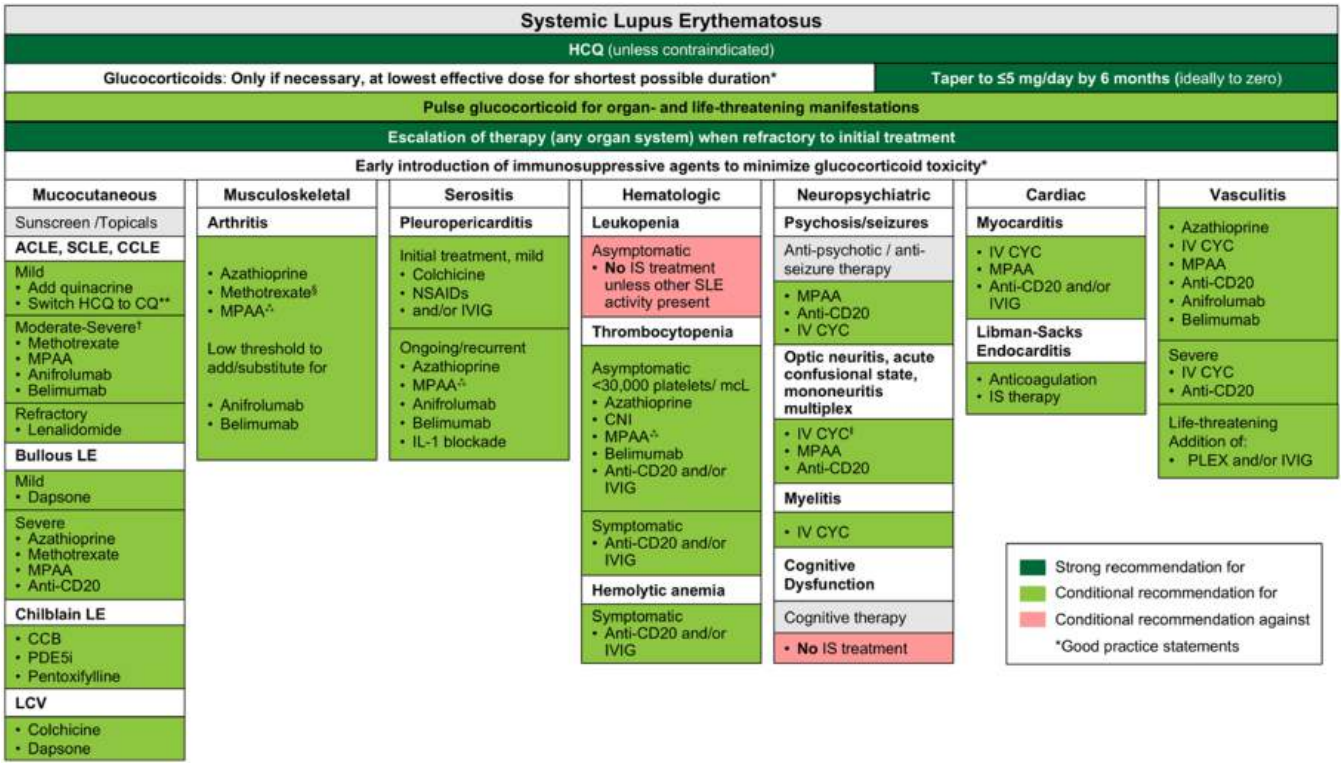

Figure 1. Overview of the recommended management for systemic lupus erythematosus (SLE). This schematic illustrates the approach to SLE treatment, with organ-specific therapies presented in separate boxes and stratified by disease severity. **The order of the medications in each box does not indicate preference unless noted otherwise.** Lupus nephritis treatment is addressed in the 2024 American College of Rheumatology Guideline for the Screening, Treatment, and Management of Lupus Nephritis.[9] **In CLE, switch HCQ to CQ with the intention of changing back to HCQ once the rash is under control. †Azathioprine may be used when pregnancy is planned. Based on the Voting Panel members' clinical experience, anifrolumab has a more rapid onset of benefit and a greater likelihood of response than belimumab. ⁂MPAA may be preferable over azathioprine. §Alternative agents such as leflunomide are occasionally used for those with arthritis. ‖Evidence for severe neurologic syndromes was largely limited to IV CYC.
ACLE, acute cutaneous lupus erythematosus; CCB, calcium channel blockers; CCLE, chronic cutaneous lupus erythematosus; CNI, calcineurin inhibitor (cyclosporin or tacrolimus); CQ, chloroquine; HCQ, hydroxychloroquine; IL-1, interleukin-1; IS, immunosuppressive therapy; IV CYC, intravenous cyclophosphamide; IVIG, intravenous Ig; LCV, leukocytoclastic vasculitis; LE, lupus erythematosus; MPAA, mycophenolic acid analogs; NSAIDs, non-steroidal anti-inflammatory drugs; PDE5i, phosphodiesterase type 5 inhibitors; PLEX, plasma exchange; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

should involve consultation with a hematologist.[65] Splenectomy is a therapy of last resort. For asymptomatic thrombocytopenia with platelet count 30-100,000/mcl, treatment is generally not indicated.[64]

Hemolytic Anemia

For <u>symptomatic</u> autoimmune hemolytic anemia (i.e., ischemic manifestations and/or hemodynamic instability) attributed to SLE, we conditionally recommend initiation of glucocorticoid therapy with IVIG and/or anti-CD20 therapy over the addition of conventional immunosuppressive agents

For mild, well-compensated hemolytic anemia, alternate therapies such as short-term glucocorticoids and conventional/biologic immunosuppressive agents may be considered.

NEUROPSYCHIATRIC MANIFESTATIONS

Neuropsychiatric SLE (NPSLE) consists of a broad range of neurologic and psychiatric manifestations that can involve any aspect of the central, peripheral, or autonomic nervous system.[66] Once ascribing signs or symptoms to SLE, an assessment of active disease (inflammatory or aPL immune-mediated) versus chronic damage should occur. In general, treatment of stroke in the setting of SLE is best directed by neurologists[67] with addition of immunosuppressive therapy when SLE-mediated inflammation is identified. We suggest a multi-disciplinary approach, including co-management with neurologists and/or psychiatrists/psychologists.

No recommendations were made for small fiber neuropathy; while found in SLE, no consensus was reached regarding immunomodulatory therapy. All agreed that this is an important research agenda item.

Table 5. Medications to treat SLE: suggested dosing and monitoring[a]

MEDICATION[a,b,c]	MONITORING	DOSING
Anakinra (Kineret®)	**CBC with differential** monthly for 3 months, then every 3 months for 3 months, then every 6 months	• Adult dosing: 100 mg SC or IV daily • Pediatric dosing: 2 mg/kg/day SC or IV daily (max 100 mg/dose). Maximum dosing of 8 mg/kg/day • Dosing for macrophage activation syndrome: 100 mg SC or IV daily, can be increased to 100 mg q 6 hours
Anifrolumab (Saphnelo®)	For adults ≥ 18 years of age, suggest at least one dose of **recombinant varicella-zoster vaccine** prior to initiation[c]	• Adult dosing: 300 mg IV q 4 weeks • Preliminary pediatric dosing: ≥ 10 years and ≥40 kg: 300 mg IV q 4 weeks. If ≥ 12 years, 300 mg IV q 4 weeks
Azathioprine (Imuran®)	**CBC with differential, AST, ALT** every 2 weeks for 8 weeks, then every 2 months **TPMT** genotyping, and **NUDT15**[d] if available, prior to initiation. Caution with allopurinol as co-administration increases azathioprine levels.	• Adult dosing: 2–3 mg/kg/day PO daily or in 2 divided doses • Pediatric dosing: 2–3 mg/kg/day PO daily or in 2 divided doses

Belimumab (Benlysta®)	**Mood changes**: Monitor for new or worsening depression or suicidal thoughts.	Adult dosing:
		• IV dosing: 10 mg/kg/dose q 2 weeks x 3 doses then q 4 weeks
		• SC dosing: 200 mg weekly
		Pediatric dosing ≥ 5 years old:
		• IV dosing: 10 mg/kg/dose q 2 weeks x 3 doses then q 4 weeks
		• SC dosing:
		  ○ 15 kg to < 40 kg: 200 mg q 2 weeks
		  ○ ≥ 40 kg: 200 mg weekly

Chloroquine (Aralen®)	**CBC with differential, AST, ALT and creatinine** at baseline and periodically **Eye Screening:** at baseline and then every 4–6 months from onset of use. **ECG:** at baseline and subsequently if at risk for QTc prolongation due to concomitant medications or cardiac risk factors for arrythmia, including Congenital Long QT Syndrome.[e]	• Adult dosing: 2.3 mg/kg/day is the maximum dosing. • Pediatric dosing: none established
Colchicine (Colcrys®)	Concomitant use of colchicine with inhibitors of CYP3A4 or P-glycoprotein efflux transporters can lead to significant increases in colchicine plasma levels. Check drug interactions prior to use.	• Adult Dosing: 0.6–1.2 mg PO daily or in 2 divided doses. Maximum dose of 3 mg daily • Pediatric Dosing: 0.6–1.2 mg PO daily or in 2 divided doses. Maximum dose of 2 mg daily
Cyclophosphamide (Cytoxan®)	**CBC with differential and creatinine** weekly for 4 weeks, then monthly **Urine pregnancy testing** for women of reproductive age prior to each infusion **Urinalysis** with infusions per local protocols and then every 6 months following completion of course **Mesna** is not routinely recommended for standard dose intravenous cyclophosphamide[f] **Urine cytology** to screen for bladder cancer if cumulative dose > 36 grams **Consult** ACR Reproductive Health Guidelines for reproductive guidance[g]	• Adult dosing: 750–1,000 mg/m^2/dose IV monthly x 6 months; maximum 1200 mg/dose • Pediatric dosing: 500–750 mg/m^2/dose IV monthly x 6 months; maximum 1200 mg/dose
Cyclosporine (Gengraf®, Neoral®, Sandimmune®)	**Creatinine, potassium, magnesium** every 2 weeks for 12 weeks, then monthly **CBC with differential**, **AST, ALT** monthly for 3 months, then every 3 months **Lipid screen** every 6 months **Blood pressure** monitoring at initiation and periodically, including when adding, modifying or discontinuing other medications	• Adult dosing: 3–5 mg/kg/day PO in 2 divided doses[h] • Pediatric dosing: same as adult dosing[h]
Dapsone	**CBC with differential, AST, ALT** weekly for 4 weeks, then every 4 weeks for 3 months, then every 3 months thereafter Check for **G6PD deficiency** before starting treatment	• Adult dosing: 50 mg PO once daily; Maximum dosing of 150 mg/day divided BID

(Continued)

Table 5. (*Cont'd*)

MEDICATION[a,b,c]	MONITORING	DOSING
		• Pediatric dosing: 1–2 mg/kg/day PO once daily. Maximum dosing of 100 mg/day
Hydroxychloroquine (Plaquenil®)	**CBC with differential, AST, ALT, creatinine** at baseline and periodically **Eye Screening:** at baseline and then annually no later than 5 years after starting treatment[l] **ECG:** at baseline and subsequently if at risk for QTc prolongation due to concomitant medications or cardiac risk factors for arrythmia, including Congenital Long QT Syndrome.[e]	• Adult dosing: 5 mg/kg/day, usually 200–400 mg daily or divided BID. Maximum dosing of 400 mg/day • Pediatric dosing: same as adult dosing
Intravenous Immunoglobulin (IVIG)	**CBC with differential** prior to first administration, then monthly if high dose to follow for hemolysis **AST, ALT, chemistry panel** prior to administration	• Adult dosing: 2 g/kg given over 2–5 consecutive days monthly • Pediatric dosing: 1 to 2 g/kg q 2–4 weeks
Leflunomide (Arava®)	**CBC with differential, AST, ALT, creatinine** monthly for 3 months, then every 3 months **Consult** ACR Reproductive Health Guidelines for reproductive guidance[g]	• Adult dosing: 10–20 mg PO daily in one dose • Pediatric dosing: • >20 kg: 10 mg PO QOD • 20-40 kg: 10 mg PO daily • >40 kg: 20 mg PO daily
Lenalidomide (Revlimid®)	**CBC with differential, AST, ALT, creatinine** at baseline, at one month and then q 2-3 months **TSH** at baseline and every 3–6 months during treatment **Urine pregnancy testing** 10–14 days and again 24 hours prior to initiating therapy, weekly during first 4 weeks of treatment, then every 2–4 weeks through 4 weeks after therapy is discontinued Please see the REMS website: https://www.lenalidomiderems.com/	• Adult dosing: 5 mg PO daily • Pediatric dosing: none established
Methotrexate (Trexall®, Rheumatrex®)	**CBC with differential, AST, ALT, creatinine** monthly for 3 months, then every 3 months **Consult** ACR Reproductive Health Guidelines for reproductive guidance[g]	• Adult dosing: 20–25 mg SC or PO once a week. Maximum dosing of 25 mg weekly • Pediatric dosing: • 15 mg/m^2 SC or PO once a week. Maximum dosing of 25 mg weekly; OR • 1 mg/kg SC or PO once a week. Maximum dosing of 25 mg weekly
Mycophenolate mofetil (Cellcept®)	**CBC with differential** with initiation and approximately 2 weeks after each dose change; regularly once on stable dosing **Urine pregnancy screen** at baseline, 8–10 days after baseline and at subsequent visits for females of reproductive potential. **Consult** ACR Reproductive Health Guidelines for reproductive guidance[g] Please see the REMS website: https://www.mycophenolaterems.com/#Main	• Adult dosing: 2–3 grams PO daily in 2 divided doses. Maximum dosing of 3 grams daily • Pediatric dosing: 300–600 mg/m^2/dose PO twice daily. Maximum dosing of 3 grams daily
Non-steroidal anti-inflammatory Drugs (NSAIDs)	**CBC with differential, creatinine, potassium** every 6 months **Blood pressure** every 12 months	Varies according to NSAID
Obinutuzumab (Gazyva®)	**CBC with differential** at 3 months, then every 6 months **IgG levels** assessed every 6 months	• Adult dosing: 1,000 mg IV on Day 1 and at weeks 2, 24, 26 and 52 • Pediatric dosing: none established
Quinacrine	**CBC with differential, complete metabolic panel** 2 weeks after starting and then 4 weeks later	• Adult dosing: 100 mg PO daily • Pediatric dosing: none available Requires compounding in the US; availability varies in other countries
Rituximab (Rituxan®) and biosimilars	**CBC with differential** at 3 months, then every 6 months **IgG levels** assessed every 6 months	Adult dosing: • 1 gram IV on Days 1 and 15

(Continued)

Table 5. (*Cont'd*)

MEDICATION[a,b,c]	MONITORING	DOSING
		Pediatric dosing: • 375 mg/m^2/dose IV weekly x 4 doses. Maximum dosing of 1 gram/dose OR • 750 mg/m^2/dose IV every 2 weeks x 2 doses. Maximum dosing of 1 gram/dose
Tacrolimus (Prograf®)	**CBC with differential, AST, ALT** monthly for 3 months, then every 3 months **Creatinine, potassium, magnesium** every 2 weeks for 12 weeks, then monthly **Lipid screen** every 6 months **Blood pressure** monitoring at initiation and periodically, including when adding, modifying or discontinuing other medications	• Adult dosing: 0.05–0.1 mg/kg/day PO in 2 divided doses[h] • Pediatric dosing: 0.2–0.3 mg/kg/day PO in 2 divided doses[h]

ACR, American College of Rheumatology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, bis in die (twice a day); CBC, complete blood counts; ECG, electrocardiogram; FDA, US Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous; NUDT15, nudix hydrolase 15; PO, orally; QOD, every other day; QT, measurement from start of Q wave to end of T wave on electrocardiogram (ventricular repolarization time); QTc, corrected QT interval; REMS, Risk Evaluation and Mitigation Strategy; SC, subcutaneous; SLE, systemic lupus erythematosus; TSH, thyroid stimulating hormone; TPMT, thiopurine methyltransferase.

[a] Dosing and monitoring listed here are suggestions and not recommendations by the Voting Panel. They are based on a compilation of data from online medication formularies, FDA package inserts for those medications with approved indications, published trial data, other relevant guidelines, and the clinical expertise of the Core and Voting Panels. As such, these suggestions may differ from other sources. Prescribing and monitoring should be tailored to individual patients, including adjustments for chronic kidney disease if indicated, and aided by the assistance of local pharmacists as needed.

[b] Please consult Table 4 for pre-treatment screening that is complementary to this guidance.

[c] We recommend routine vaccinations for all patients prior to starting immunosuppressive therapy, if possible. Please consult Table 4 and the following guideline for vaccination in patients with rheumatic and musculoskeletal disease: Bass AR, Chakravarty E, Akl EA, et al. 2022 American College of Rheumatology Guideline for vaccinations in patients with rheumatic and musculoskeletal diseases. *Arthritis Care Res (Hoboken)* 2023;75 (3):449–464.

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[g] Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol* 2020;72 (4):529–556.

[h] Therapeutic levels are based on literature in transplant patients. There are minimal data in SLE patients. Trough levels can be used for adherence and toxicity assessments.

[i] Rosenbaum JT, Costenbader KH, Desmarais J, et al. American College of Rheumatology, American Academy of Dermatology, Rheumatologic Dermatology Society, and American Academy of Ophthalmology 2020 joint statement on hydroxychloroquine use with respect to retinal toxicity. Arthritis Rheumatol 2021;73:908-911.

Severe Neuropsychiatric Syndromes

For active lupus optic neuritis -OR- lupus acute confusional state -OR- active mononeuritis multiplex, we conditionally recommend initial therapy with pulse/high-dose glucocorticoid taper plus IV CYC, MPAA, or anti-CD20 therapy over pulse/high-dose glucocorticoid monotherapy alone

For active lupus myelitis, we conditionally recommend initial therapy with pulse/high-dose glucocorticoid plus IV CYC over pulse/high dose glucocorticoid with other non-CYC immunosuppressive agents

For active lupus psychosis, we conditionally recommend anti-psychotic therapy plus glucocorticoid, IV CYC, MPAA, or anti-CD20 therapy over anti-psychotic therapy alone

Evidence for severe neurologic syndromes was largely limited to IV CYC, and level of certainty was very low. Voting Panel members opted to include MPAA and anti-CD20 therapy as options based on their clinical experience, the wide spectrum of severity in these syndromes, and the desire to avoid or limit use of IV CYC especially in young women of reproductive age. Glucocorticoid-induced psychosis may confound the assessment of clinical response to immunosuppressive therapy. When using IV CYC, we consider treatment with 3 monthly infusions followed by an alternative immunosuppressant, usually MPAA, to minimize the risk of potential toxicities, including impaired fertility. An ischemic etiology that might require anticoagulation, or the presence of an alternative diagnosis such as neuromyelitis optica spectrum disorder or myelin oligodendrocyte glycoprotein antibody disease, should be ruled out as these may impact therapy. Plasma exchange (PLEX) and/or IVIG are reasonable additional therapies for severe or refractory disease.[68,69]

Seizures

For seizures attributed to active SLE, we conditionally recommend anti-seizure therapy plus glucocorticoid, IV CYC, MPAA, or anti-CD20 therapy over anti-seizure therapy alone

It is important to rule out fixed neurologic damage (i.e., scarring) rather than active inflammation as the etiology for seizures. Decision for a particular therapy may vary depending on concomitant SLE manifestations, as well as clinician and patient preferences.

Cognitive Dysfunction

For isolated cognitive dysfunction attributed to SLE and documented by neuropsychological testing, we conditionally recommend *against* adding immunosuppressive therapy (including glucocorticoid) to cognitive therapy over using cognitive therapy alone

Neuropsychological testing should be performed to document cognitive dysfunction (or decline) that is potentially attributable to SLE and to rule out other identifiable or treatable etiologies. The efficacy of immunosuppressive therapy (including glucocorticoid) for isolated cognitive dysfunction in the absence of inflammatory signs (e.g. abnormal CSF or imaging studies) has not been demonstrated and so is not recommended; alternative pharmacological and non-pharmacological therapies are under study,[70,71] however some clinicians may choose to add immunosuppressive therapy if active lupus inflammation is strongly suspected. Cognitive dysfunction associated with other recognized NPSLE syndromes (e.g., acute confusional state, psychosis) that are characterized by an immunologic or inflammatory etiology should be treated with immunosuppressive therapy, as detailed in preceding recommendations.

MUCOCUTANEOUS MANIFESTATIONS

Most reports of therapy for cutaneous lupus combine acute with subacute/chronic rash in the treatment group; as a result, these are grouped together here for most recommendations. Diagnosis and classification are reviewed elsewhere.[72] Treatment for alopecia, acknowledged by the Patient and Voting Panels as a common and distressing SLE manifestation, is not addressed with a specific recommendation due to its multifactorial nature.[73] Dermatology evaluation should be considered.

***GPS*: People with SLE should be educated on the use of sunscreen and other sun-protection measures to reduce risk of rash and potential disease flare**

***GPS*: Initial therapy for cutaneous lupus rash—in addition to HCQ—should be topical, including glucocorticoid and/or calcineurin inhibitors (Table [6]). Initial therapy may also include a course of intralesional glucocorticoids and/or a brief course of oral glucocorticoids**

Sunscreens should block both UVB and UVA light: Sun Protection Factors of ≥70[74] for chemical and ≥50 for physical blocker-based sunscreens are recommended. Physical blocker sunscreens may be preferable in allergy-prone people.[75] Clinicians should provide counseling on proper sunscreen use,

Table 6. Suggested topical therapies for cutaneous lupus

Glucocorticoid topical therapies	Agent	Body Location	Comments
Super-potent Very high	Augmented betamethasone dipropionate (solution) Clobetasol propionate Halobetasol propionate	Scalp Body	For body: BID for refractory lesions then switch to BID moderate potency agent
High	Betamethasone dipropionate Fluocinonide Halcinonide Mometasone furoate		
Moderate	Betamethasone valerate Fluocinolone acetonide (0.025%) Triamcinolone acetonide Hydrocortisone valerate (0.2%)	Body	Use for longer term treatment on body after initial high or very high potency
Low	Desonide (0.05%) Fluocinolone acetonide (0.01%) Hydrocortisone {0.5-2.5%)	Face	Short term only
Non-glucocorticoid topical therapies			
Calcineurin Inhibitors	Pimecromus cream Tacrolimus ointment	Face	No limit to duration of use
JAK Inhibitors (off label)	Ruxolitinib Tofacitinib		

There is no significant difference in which topical options should be used for different cutaneous lupus subtypes, except for lupus panniculitis (topical glucocorticoids will not reach the fat, the area of inflammation in panniculitis). Body location guides the choice of topical agents. Generally, avoid use of fluorinated glucocorticoids on the face except for a few days if severe flare. Topical therapies are generally used BID. More potent topicals are generally used for up to 2 weeks duration (not on the face however) and then switched to less potent topical agents. Solutions are favored for scalp; creams or ointments for elsewhere (patient preference). BID, twice a day.

including reapplication, sun avoidance techniques, and alternative sun-protection methods (e.g., sun-protective clothing). Dermatology evaluation in people with significant skin disease is encouraged; lesional skin biopsy is suggested when needed to guide therapy or to rule out other diagnoses and should ideally be interpreted by a dermatopathologist.

Prevention of skin scarring was a high priority for the Patient Panel, especially in visible areas such as the face. Low-potency glucocorticoids can be used for active disease for a limited time on the face, but higher-potency glucocorticoids should be used only for a few days due to risk of skin atrophy. Involvement of non-facial or non-intertriginous areas of the body can be treated with moderate or higher potency topical glucocorticoids. Topical calcineurin inhibitors can be used without restriction. Suggestions for topical therapy of cutaneous manifestations are summarized in Table 6; these are not formal recommendations. Table 6 is a summary of general information provided as a convenience for the clinician utilizing the formal treatment recommendations, in order to help guide choice of specific topical therapy.

Acute, Subacute, and Chronic Cutaneous Lupus

For mild, ongoing, and skin-predominant lupus despite treatment with HCQ and/or topical therapies, we conditionally recommend adding quinacrine or switching to chloroquine over adding an immunosuppressive agent

Change in antimalarial therapy is a common dermatology practice, as it may improve mild rash without the need for more aggressive therapy. Quinacrine is not associated with increased retinopathy risk and is available through compounding pharmacies at variable cost; addition of quinacrine is preferred over a switch to chloroquine, given that chloroquine has a higher risk for retinal toxicity than HCQ.[76,77] For chloroquine, we suggest every 4–6-month retinal monitoring (Table 5); this differs from the American Academy of Ophthalmology's yearly recommendation[78] and is based on an increasing appreciation of chloroquine risk from both clinical experience and published evidence.[76,77] Chloroquine is an option in patients without major risk factors for retinopathy (Table 5), with the intention to change back to HCQ when rash is better controlled.

For ongoing moderate-severe cutaneous lupus refractory to topical and antimalarial therapies and/or oral glucocorticoid necessitating escalation of therapy, we conditionally recommend the addition of methotrexate (MTX), MPAA, anifrolumab, and/or belimumab

The Patient Panel placed a very high priority on scar prevention. The choice of specific therapy should be based on severity of lesions, risk for scarring, comorbidities, and patient preference. The Voting Panel voted against prioritizing specific conventional or biologic immunosuppressive agents due to limited data and a difference of opinion among panel members. MTX and MPAA are the preferred conventional agents, but AZA may be used when pregnancy is planned. There are no comparative effectiveness studies of the FDA-approved biologics anifrolumab and belimumab for cutaneous SLE. Both may be beneficial;[79–82] however, panel

members emphasized their clinical experience with anifrolumab's rapid onset of benefit and greater likelihood of response.[80]

For ongoing moderate-severe cutaneous lupus refractory to topical therapies, antimalarials, and conventional and/or biologic immunosuppressive agents necessitating escalation of therapy, we conditionally recommend adding or substituting lenalidomide

Lenalidomide is suggested as a potential therapy of "last resort" despite the potential teratogenicity and thrombosis risk;[83–85] prescribers must participate in the Risk Evaluation and Mitigation Strategy (REMS) program.

Bullous Lupus Erythematosus

For mild ongoing bullous lupus despite treatment with topical therapies and antimalarial therapies, we conditionally recommend the initial addition of dapsone over initiation of glucocorticoid

Metabolites of dapsone may lead to hemolytic anemia, methemoglobinemia, or other hematologic issues; G6PD should be assessed prior to start of therapy, with appropriate monitoring during use[86,87] (Table 5).

For moderate-severe bullous lupus refractory to topical therapies, antimalarials, and/or oral glucocorticoid necessitating escalation of therapy, we conditionally recommend adding a conventional immunosuppressive (MPAA, MTX, AZA) and/or anti-CD-20 therapy

The Voting Panel relied on indirect evidence from pemphigus due to its similar disease process. Trials in pemphigus support either glucocorticoids with conventional immunosuppressive or anti-CD20 therapy for bullous diseases.[88,89]

Chilblain Lupus

For chilblain lupus, despite symptomatic, topical, and antimalarial therapies, we conditionally recommend the addition of pentoxifylline, phosphodiesterase type 5 (PDE5) inhibitors (e.g., sildenafil, tadalafil), and/or calcium channel blockers (e.g., nifedipine) over initiation of immunosuppressive therapies

Topical therapies for chilblain lupus may include glucocorticoid, calcineurin inhibitors, and topical nitrates. Most evidence reviewed was low-level and indirect, from primary chilblains. The role of immunosuppressive therapy is unclear.[90,91]

Leukocytoclastic Vasculitis

For mild ongoing cutaneous vasculitis despite topical and antimalarial therapies, we conditionally recommend the addition of dapsone or colchicine over immunosuppressive therapies, including oral glucocorticoid

The Voting Panel emphasized avoiding overtreatment of minor cutaneous vasculitis. Extensive or severe cutaneous vasculitis, however, generally requires glucocorticoid or immunosuppressive treatment.

SEROSITIS

Pleuropericarditis

For pleuropericarditis, we conditionally recommend initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or their combination, with a low threshold for escalation to glucocorticoid therapy, over initiating glucocorticoid therapy alone

For ongoing/recurrent episodes of lupus pleuropericarditis despite treatment with HCQ, NSAIDs, colchicine, and/or glucocorticoids necessitating escalation of therapy, we conditionally recommend conventional (MPAA, AZA) or biologic immunosuppressive therapies over initiating/increasing glucocorticoid monotherapy

Recommendations for pericarditis and pleuritis are combined, given similarities in management. NSAIDs and colchicine may be used together as initial therapy, and oral glucocorticoid added as needed. Evidence was of low certainty and inadequate to direct clinicians regarding use of conventional versus biologic therapies; however, severe or worsening disease necessitates rapid escalation of immunosuppressive treatment. Escalation to immunosuppressive therapy for ongoing/recurrent symptoms reflects the desire to avoid complications from pleuropericarditis and prolonged glucocorticoid use.

The Voting Panel's preferred biologic therapy for predominant pleuropericarditis is interleukin-1 (IL-1) blockade, for which there is primarily indirect evidence for SLE;[92–98] a decision to use IL-1 blockade may depend in part on presence or absence of other SLE manifestations as well as cost and

accessibility issues. Limited data support potential roles for other biologic agents.[79,81]

MUSCULOSKELETAL

Arthritis

GPS: Therapy for acute or recurrent episodes of inflammatory arthritis in people with SLE may include a course of NSAID or a limited course of oral glucocorticoid while waiting for long-term therapies to take effect

Joint involvement occurs in up to 95% of those with SLE,[99,100] resulting in permanent joint damage in 11.7%.[101] It is associated with lower quality of life and work disability.[102,103] Lupus-related joint involvement ranges from arthralgia to deforming arthropathy and erosive arthritis. While NSAID and glucocorticoids are useful in providing rapid symptom relief, the goal of therapy is management with longer-term disease-modifying agents.

For persistent or recurrent active SLE arthritis in people taking HCQ, regardless of prior/current NSAIDs or short-term glucocorticoid therapy, we conditionally recommend initial therapy with MTX, MPAA, or AZA, with a low threshold to add or substitute with belimumab or anifrolumab for inadequate response, over initial biologic therapy

The recommendation for the treatment of lupus arthritis is conditional due to the widely varying clinical practice patterns and preferences among panelists. There will be individuals for whom initial biologic therapy[79,104,105] with belimumab or anifrolumab is considered preferable, or for whom combination (conventional plus biologic) therapy is required. For people with predominant arthritis without a history of significant other organ involvement, MTX may be considered first; for those with history of or current other organ involvement, MPAA might be preferable. A randomized controlled trial in patients with moderate-to-severe active (extra-renal) lupus disease activity compared overall disease activity response in patients randomized to MPAA versus AZA. While the study was not powered for specific organ response, those treated with MPAA had significantly higher rates of remission, shorter times to achieving remission, and fewer side effects than did those receiving AZA, suggesting MPAA may be preferred over AZA as initial therapy when conventional immunosuppressives are planned.[106] AZA is preferred for those planning pregnancy.

Alternative agents such as leflunomide or other therapies approved for rheumatoid arthritis treatment are occasionally used when arthritis is the predominant feature. The Voting Panel emphasizes early escalation/change in therapy for inadequate response. Shared decision-making is vital; Patient Panel members placed a high value on consideration of specific side effects and tolerability for any given therapy.

Jaccoud Arthropathy

Jaccoud arthropathy was discussed but no consensus was reached on surgical or medical therapy, given the paucity of data[107] and clinical /patient experience. Voting Panel members suggest referral to occupational/physical therapy, splinting, or bracing; all agree this is an area for future research.

SYSTEMIC VASCULITIS

For vasculitis attributed to active SLE, we conditionally recommend initial therapy with pulse/high-dose glucocorticoid taper and conventional (IV CYC, MPAA, AZA) or biologic (anti-CD 20 therapy, belimumab, anifrolumab) immunosuppressive therapy

For severe vasculitis attributed to active SLE, we conditionally recommend IV CYC or anti-CD20 therapy as initial therapy over other immunosuppressive therapies

For life-threatening vasculitis attributed to active SLE (e.g., diffuse alveolar hemorrhage or mesenteric vasculitis), we conditionally recommend the addition of PLEX and/or IVIG to pulse/high-dose glucocorticoid taper and immunosuppressive therapy, over no additional therapy

Pulse/high-dose glucocorticoid and immunosuppressive therapies are recommended for vasculitis due to the high risk of organ- and life-threatening outcomes. The evidence was of very-low certainty and primarily addressed treatment for mesenteric vasculitis, diffuse alveolar hemorrhage, and retinal vasculitis. PLEX and IVIG are suggested as adjunctive therapies to high-dose glucocorticoid and immunosuppressive agents for life-threatening vasculitis.[108,109] Shared decision-making is emphasized.

CARDIAC MANIFESTATIONS

Myocarditis

For acute or worsening lupus myocarditis, we conditionally recommend treatment with glucocorticoid and IV CYC, MPAA, or anti-CD20, and/or IVIG over glucocorticoid monotherapy

The treatment of lupus myocarditis relies on a combination of glucocorticoids and immunosuppressants in addition to heart failure

therapy. Cyclophosphamide and MPAA have the most evidence to support their use; however, positive reports from case-series also substantiate treatment with anti-CD-20 and IVIG. No randomized controlled trials are available to guide decision-making.[110–112]

Non-Bacterial (Libman-Sacks) Endocarditis

For non-bacterial (Libman-Sacks) endocarditis,[113] we conditionally recommend anticoagulation and/or immunosuppressive therapy (including glucocorticoid) over no medical therapy

The decision for medical therapy should be based on discussion with cardiologists and reflect the risk for embolization. A decision regarding potential use of immunosuppressive therapy may be informed, in part, by evidence for SLE activity in other organ systems. Non-bacterial (Libman-Sacks) endocarditis is closely associated with the presence of aPL (valvular heart disease constitutes a clinical domain in the 2023 ACR/EULAR antiphospholipid classification criteria[114]) and anticoagulation is generally suggested. A small case series (n=17) noted significant improvement in valvular function and reduction in vegetation size with combined conventional anti-inflammatory and antithrombotic therapy.[115] However, it should be noted that in this series only 9 of 17 patients were treated with immunosuppression; 5 patients died, 2 of infection (it is not clear whether they were on immunosuppressive therapy). Surgical valve replacement is usually required for severe disease.

DISCUSSION

In this guideline, we recommend HCQ, limiting glucocorticoid exposure, and early introduction of conventional and/or biologic immunosuppressive therapies to achieve remission or low disease activity while minimizing medication toxicity for all people with SLE. Many recommendations are conditional and do not specify one particular immunosuppressive agent, or even one class of agent. This is a direct result of the limited evidence available, variations in treatment approach among the Voting Panel members, and the high value Patient Panelists placed on the impact of side effects and tolerability for any given therapy. Thus, we strongly emphasize the role of shared decision-making between patients and clinicians because multiple factors impact therapy choice. Shared decision-making allows people with SLE to choose optimal medications in terms of efficacy, tolerability, and availability. This yields the added benefit of enhancing medication adherence, an important goal since this ultimately is a critical determinant of any therapy's effectiveness. Likewise, routine assessment of medication adherence is suggested. Self-report, electronic health record-based automated adherence monitoring, or measuring blood levels merit future research.

Shared decision-making was also a major theme throughout the Patient Panel discussion, reflecting the importance of fostering trust and respect for patient values and priorities. These priorities, influenced by a person's life stage and disease state, change over the course of the disease and should be regularly explored. Other highlighted themes included judicious glucocorticoid use to minimize adverse effects and a strong desire for patient involvement and partnership in research, from planning to execution, to ensure trials include representative cohorts and address patient needs.

Both provider and patient panel members cited difficulties in accessing care and medications due to a range of barriers. We acknowledge that diverse healthcare settings with varied access to medications and care providers is a critical issue contributing to racialized and socioeconomic disparities. With these recommendations, we aimed to reduce health care disparities by providing an evidence-based standard for patient-centered care.

Current gaps in the SLE literature helped identify important areas of future research (Supplementary Materials 7). Comparative effectiveness trials within specific organ systems, in addition to well-designed observational and cohort studies, will inform future guideline treatment recommendations.

Clinical rheumatologists and rheumatology teams are vital in the care of people with SLE. This guideline provides direction for therapeutic decisions after clinician-patient discussion; it also encourages close working relationships between rheumatologists (or expert rheumatology teams) and the other medical specialists integral to providing comprehensive and collaborative lupus care.

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