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

Public Comments

The American College of Rheumatology (ACR) Guideline for Treatment of Systemic Lupus Erythematosus (SLE) *call for public comment was posted on the ACR website January 4, 2024. The announcement was emailed to the Practice Guidelines Subcommittee, Quality of Care Committee, and ACR Board of Directors, and was included in multiple ACR publications and on ACR social media platforms. Twenty-four (24) responses were received via the online form. The public comment period closed on February 3, 2024.*

RESPONSES RECEIVED ONLINE:

- Name: Rosalind Ramsey-Goldman
- Institution: Northwestern University Feinberg School of Medicine
- Position: Professor of Medicine
- Disclosure (optional):
  - Speaker honoraria from 15th International Lupus Meeting Seoul Korea and Georgetown University.
  - Committee chair honoraria from American College of Rheumatology.
  - Consulting for Ampel Solutions, Aurinia, Biogen, Bristol Myers Squibb Company, Calabetta, Clarivate, Exagen, Merck KgaA, Sysracuse University, Upstart Research Consulting.

Comment:

This proposal is impressive and comprehensive for what is available in the literature. However, health disparities are not mentioned explicitly either as a separate entity of within the PICO questions outlined in the proposal. I am concerned that the findings from this project will not apply to the comprehensive range of lupus patients we want to reach. Most of the extensive literature on health disparities is not in clinical trials, which in itself is a problem, but is available in observational and epidemiologic studies, and called out in quality indicator assessment. cohort studies. It is important to add this topic to the search even if it means the message is that this important information is lacking in guidelines, and thus, needs to be addressed in future research so that all patients have an opportunity to receive the diagnostic and therapeutic care recommended in the guidelines. You have a diverse panel of junior to senior experts on the team which is commendable. The American College of Rheumatology strives to be the leader not only in the Americas, but also worldwide. The recently formed Global Engagement Committee is an example of how the organization wants to foster an international presence and awareness.

Along those lines, another issue to consider is getting the voices of providers from other countries (you already Canadian and South American representation) on the panel. At a recent symposium on Lupus in Africa sponsored by the Systemic Lupus International Collaborating Clinics (SLICC) group, we asked the invited speakers how we could work together, and their comment was our voices are missing in published guidelines because we are not represented in these activities. Even though the current effort is sponsored by the ACR, there is a lot to learn about how diseases are managed internationally, as we too, have resource challenged areas where care cannot meet guidelines or diagnostic criteria, i.e., ANA positivity required for EULAR/ACR classification, where getting an ANA is virtually impossible or getting access to a renal biopsy as another example. These challenges discussed by diverse voices might result

in innovative ideas on how to better care for marginalized patients with lupus in this context of limited resources.

- Name: Farshid Bozorgnia
- Institution: University of California Irvine
- Position: Assistant professor
- Disclosure (optional): Nothing to disclose

Comment:
Respondendent skipped this question

- Name: Hanan Ibrahim
- Institution: University of Missippi Medical Center
- Position: Assistant Professor
- Disclosure (optional): Nothing to disclose

Comment:
- Nice and smooth outline, excited for it.
- I would recommend adding a paragraph defining what partial recovery, recovery, and refractory LN are.
- I would recommend commenting on the timing of starting the transplant evaluation.
- I would recommend adding data on the combination of Belimumab and a CNI.
- I would recommend adding a section on HCQ dosing in severe CKD or ESRD patients.
- I would recommend adding a section on the use of steroids in the setting of psychosis and the implications of that.

- Name: Murray Urowitz
- Institution: University of Toronto
- Position: Professor Emeritus, Temerty Faculty of Medicine
- Disclosure (optional): Nothing to disclose

Comment:
The plan is comprehensive and certainly encompasses the important presentation senarios and therapeutric options. In the outcome objectives you always include:
Reduction of proteinuria
Preservation of kidney function
I expect these would be more specifically defined. For example for reduction in proteinuria - CRR (<500mg/24 hrs); PERR (<700mg) or reduction by 50%
For preservation of kidney function maintenance of eGFR or by reduction by 10% 0r less or by 20% or less

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In the membershgip on the oversight committee, I did not see people who have developed large cohorts followed for many years eg Michelle Petri, Zahi Touma, Sam lim, Bernardo Pons-Estel

- Name: John FitzGerald
- Institution: UCLA
- Position: Clinical Chief
- Disclosure (optional): Nothing to disclose

Comment:
Comprehensive document. While it appears renal focused, I do see other SLE topics addressed but not as clearly developed.

- Name: Philip Seo
- Institution: Johns Hopkins University
- Position: Associate Professor of Medicine
- Disclosure (optional): None provided

Comment:
Could this become a joint project with the ASN? I think it's always confusing when the ACR and ASN come out with separate recommendations for LN.

- Name: Andrew Laster
- Institution: Arthritis & Osteoporosis Consultants of the Carolinas
- Position: President
- Disclosure (optional): Nothing to disclose

Comment:
Did not see a PICO question related to use of analytes to assess disease activity and monitor response to drug therapy. Specifically, does measurement of complement fragment binding to erythrocytes, B cells and/or platelets alter clinical outcomes in SLE including LN ? Could be expanded to include measurement of antibodies to dsDNA and C1q.

- Name: Rahul Patel
- Institution: ImmPACT Bio
- Position: Executive Medical Director

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- Disclosure (optional): Am an employee of a biotech company developing cell therapy treatments for SLE and LN.

Comment:
Overall, a much needed and important effort!

Some general suggestions - regarding patient panel, suggest approaching Lupus and Allied Disease Association (LADA) and Lupus Research Alliance patient groups.
Suggest some discussion about endpoints, in particular LN endpoints and limitations of complete renal response and partial renal response and current landscape of endpoints that may better reflect disease quiescence/adequate control. Suggest mention of emerging (pending) updates to histopathologic renal classification criteria of LN as well.

On treatment management, especially Class III/IV, that is refractory to initial induction or maintenance measures, suggest some discussion about role of clinical trials, what type of proliferative LN patient should be considered for clinical trials, and in particular, CAR T studies.

Suggest including some general 'special' case areas for discussion - rapidly progressive GN, pregnancy or treatment of LN/SLE in women of childbearing potential, and associated APLAb, as well as patient populations with known more severe disease.

Lastly, role of healthcare disparities and impact on SLE - that is a topic in and of itself, but some mention on how those may impact and influence management and even potential implicit biases that could influence management of SLE/LN.

- Name: Frank Trudo
- Institution: AstraZeneca
- Position: Vice President US Medical, Respiratory & Immunology
- Disclosure (optional): Employee and shareholder, AstraZeneca

Comment:
Dear American College of Rheumatology,

Thank you for the opportunity to review the ACR Lupus Guidelines Project Plan as part of the Call for Public Comment. AstraZeneca appreciates ACR's efforts in updating the treatment guidelines to improve the care for SLE patients. Please find our comments below for your review and consideration.

If I may be of further assistance to you or you have any questions regarding the comments, please contact AstraZeneca at 1-800-236-9933.

Kind Regards,
Frank Trudo, MD

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

Public Comments

Vice President, US Medical, Respiratory and Immunology
AstraZeneca, LP
Medical Affairs
1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437

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1. Section: C. Medications: Overview and Special Considerations. Page 33-34 Line 929-967
   Questions P30 & P31 seek to investigate if initiating immunosuppressive therapy with a steroid taper results in better clinical outcomes and fewer adverse medication effects for patients with Systemic Lupus Erythematosus (SLE).

   Consider including biologics as an intervention for P30 & P31.

2. D. Guiding Therapy Principles: Page 35-36 Line 1036-1043 Given the positive impact of remission and low disease activity (LDA) on clinical outcomes,1 consider emphasizing the importance of remission and LDA as treatment goals, including providing recommended standardized definitions to target.2

   Consider the inclusion of a Populations/patients, Intervention, Comparator, and Outcomes (PICO) question to investigate the impact of various treatment strategies (including but not limited to immunosuppressives and biologics) on achieving remission or LDA. References: 1.Parra Sanchez AR, Voskuyl AE, van Vollenhoven RF. Treat-to target in systemic lupus erythematosus: advancing towards its implementation. Nat Rev Rheumatol. 2022;18:146-157. 2.Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis. 2024;83:15-29.

3. D. Guiding Therapy Principles: Page 35-36
   SLE is associated with significant impairment of health-related quality of life and patient-reported outcomes are important measures to evaluate.1

   Consider the addition of a PICO question to investigate the impact of treatment interventions (including but not limited to hydroxychloroquine (HCQ), immunosuppressants, and biologics) on quality of life and patient reported outcome measures, such as Lupus QoL and SF-36. Reference: 1.Olesinska M, Saletra A. Quality of life in systemic lupus erythematosus and its measurement. Reumatologia. 2018;56:45-54.

4. D. Guiding Therapy Principles: Page 35-36
   SLE is more prevalent in African American, Asian/Pacific Islander and Hispanic populations and can be associated with more severe manifestations.1 Additionally, race and ethnicity may impact response to treatment.

   Consider the inclusion of a PICO question to investigate if the efficacy and safety of SLE treatments vary due to differences in race and ethnicity. Reference: 1. Parodis I, Lanata C, Nikolopoulos D, et al. Reframing health disparities in SLE: a critical reassessment of racial and ethnic differences in lupus disease outcomes. Best Practice Res Clin Rheumatol. In Press.

5. D. Guiding Therapy Principles: Page 35-36
   Socioeconomic status impacts both the burden of SLE and access to appropriate treatments and is an important consideration when striving for equitable care.1

   Consider highlighting these considerations in the Guiding Therapy Principles Section to ensure practitioners are addressing equitable treatment across socioeconomic status
   Reference: 1.DeQuattro K, Yelin E. Socioeconomic status, health care, and outcomes in systemic lupus erythematosus. Rheum Dis Clin N Am. 2020;46:639-649.

6. E1. Constitutional Symptoms: Page 37 Line 1096-1103
   Fatigue is one of the most common and bothersome symptoms of SLE.1

   Consider the addition of a PICO question to investigate the impact of SLE treatments (including but not limited to HCQ, immunosuppressants, and biologics) on fatigue.
   Reference: 1.Kawka L, Schlencker A, Mertz P, et al. Fatigue in systemic lupus erythematosus: an update on its impact, determinants and therapeutic management. J Clin Med. 2021;10:3996.

7. E2. Hematologic Manifestations: Page 37 Line 1111-1131
   For Question P37, consider the addition of biologics in both intervention groups:
   For non-immunosuppressed patients: addition of
   • Azathioprine
   • MMF/MPA
   • Glucocorticoid
   • Biologics
   For patients on immunosuppressants:
   • Stopping or lowering immunosuppressive therapy
   • Addition of biologics to current immunosuppressants

8. E3. Neuropsychiatric Manifestations: Page 40
   Neuropsychiatric diseases are more common in patients with SLE than in the general population,

with major depression being reported in 24% of SLE patients.1

Consider the addition of a PICO question to investigate the impact of SLE treatments (including but not limited to HCQ, immunosuppressants, and biologics) on depression and suicidality.
Reference: 1. Zhang L, Fu T, Yin R, et al. Prevalence of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. BMC Psychiatry. 2017;17:70.

9. E4. Cutaneous/Mucocutaneous: Page 51 Alopecia is a frequent occurrence in SLE and can be distressing to patients.1,2

   Consider the addition of a PICO question to investigate the impact of systemic treatment interventions (including but not limited to HCQ, immunosuppressants, and biologics) on SLE-associated alopecia. References: 1.Concha JSS, Werth V. Alopecias in lupus erythematosus. Lupus Science Med. 2018;5:e000291. 2.Klein R, Moghadam-Kia S, Taylor L. Quality of life in cutaneous lupus erythematosus. J Am Acad Dermatol. 2011;64:849-858.

- Name: Herson Quiñones
- Institution: GSK
- Position: Vice President, US Medical Affiars, Specialty, COVID and Pipeline TA Head
- Disclosure (optional): Employee of GSK

Comment:
GSK appreciates the opportunity to provide feedback on the ACR Lupus Guidelines-Project Plan for public comment. GSK comments, as detailed below, include both specific comments and additional considerations on the project plan.

Specific comments to the project plan:

1. Page 11, Line 339-351 a. We suggest the Guidelines address the use of BEL+MMF/MPA vs MMF/MPA and BEL+CYC vs CYC in these populations as part of this PICO question

2. Page 11, Line 352 a. We suggest the Guidelines address the optimal therapy for cases of proteinuria >3g/d and for proteinuria <3g/d?

3. Page 13, Line 370-375 a. We suggest the Guidelines clarify the timing of 6 months and 12 months (i.e. is this a total of 6/12 month of therapy? Or 6 and 12 months following the completion of initial/induction therapy)

4. Page 13, Line 377 a. We suggest the guidelines include review of the use of belimumab as part of the "initial" therapy of Intervention (X) Column, or that this column is clarified as "Following initial MMF/MPA therapy, alone or in combination"

5. Page 16 and 17, under line 401(intervention/comparator table for class V) a. This table lists any CYC+BEL vs CYC alone and MMF/MPA+BEL vs MMF/MPA alone, and other combinations with BEL. We suggest these combinations with BEL also be added explicitly for Class III and IV LN

6. Page 18, Line 426 a. We suggest a specific definition for kidney preservation be defined. Should this be eGFR change from pre-flare? Baseline values? Based on biopsy?

7. Page 20, Line 448 and 449 a. We suggest definitions for CRRs and PRR be provided, as well as the definition of these measures in relevant clinical trials

8. Page 33, Line 937 and 956 a. We suggest that the Guidelines explicitly state what "immunosuppressive therapy" options include to help differentiate the use of traditional immunosuppressants from biologics/novel therapies

9. Page 40, line 1223 a. We suggest that the Guidelines include belimumab in the Interventions for which literature is searched

10. Page 41, Line 1259 a. We suggest that the Guidelines include belimumab in the Interventions for which literature is searched

11. Page 46 line 1457 a. We suggest that the Guidelines include belimumab in the Interventions for which literature is searched

12. Page 51 Line 1682 a. We suggest that the Guidelines include belimumab in the Interventions for which literature is searched

Additional considerations regarding the project plan:
1) Will the ACR elucidate how remission is defined (e.g., CRR, PRR, PERR, DORIS, etc)?
2) Will there be any consideration to including the concept of disease modification which has been successfully applied in other autoimmune conditions?
3) Please clarify whether there will be additional opportunities for feedback as the guidelines are developed.

- Name: Jaime Guzman
- Institution: University of British Columbia
- Position: Clinical Associate Professor
- Disclosure (optional): Nothing to disclose.

Comment:
Vancouver, Canada, 2 of February 2024
RE: ACR proposal for lupus Guidelines Via online submission

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

Public Comments

Dear Sir or Madam: I read with interest the proposal for the ACR systemic lupus erythematosus practice guidelines posted in the website. As expected, the overall methods appropriately adhere to the GRADE methodology adopted by the ACR, but in my opinion there are some omissions and lack of clarity in important sections. I believe there needs to be more clarity in the scope of the guideline and how it was decided, and in how the PICO questions were developed to make sure they address the right questions. I have organized my thoughts around the four points below. My apologies if I missed the information, I have to confess that I did not read all the appendices in detail.

My first point is that it is not clear whether, or to what extent, the guidelines will apply to children with lupus. As a pediatric rheumatologist I believe this is the greatest omission. Nowhere there is a clear statement of whether this guideline is meant to apply to children with lupus or not. If the decision is that childhood lupus is out of the scope of these guidelines, this needs to be stated upfront, so that nobody attempts to apply them indiscriminately to children. Personally, I think it would be a great shame excluding children from this guideline. Further, whatever the decision, there needs to be transparency as to how the decision was reached.

I believe the best scenario is that the guidelines make appropriate allowance for childhood lupus. There are at least 3 well established reasons why a given recommendation may differ for children with lupus:
• Lupus presents differently in children and is usually more severe.
• Children have much less co-morbidities than adults, which impacts treatment choices.
• Treatment decisions in childhood lupus must consider their current state of growth and development and how proposed treatments may impact them.

Given the above, it is clear to me that the applicability of a given recommendation to children needs to be carefully considered and stated in the guidelines, at least for the recommendations most impacted by the 3 reasons above.

There are several options for mechanisms to ensure due consideration of childhood lupus in these guidelines:
• Having a pediatric voting panel or enough representation of pediatric clinicians (Pediatric Rheumatology, Nephrology, others) in the current voting panel.
• Making sure pediatric lupus research is included in the literature review.
• Explicit voting on which recommendations also apply to children with lupus and which ones do not.
• Considering if some PICO questions should be added to specifically address childhood lupus concerns.

My second points is the lack of clarity on how the PICO questions were developed. This is important to reassure the reader that the relevant perspectives were duly considered. There is not detail on how it was ensured that the proposed PICO questions are the right ones, the ones that really matter to patients and clinicians.

My third point is that there is a lot of appropriate attention on appraisal of the evidence but not enough attention on how those appraisals will translate into recommendations. It is very likely that for many PICO questions there will be scant high-quality evidence, especially since there is few if any clinical trials dealing with the most common treatments currently in use. It would be great to devote more care and thought as to how the team will ensure that recommendations made by the voting panel when there is

little evidence will do more good than harm. Was the voting panel selected with this in mind? Is there a good mix of clinicians from different backgrounds, different specialties, different practice environments, etc? Are there patient representatives of different backgrounds and different ages? Are mechanisms in place to prevent groupthink and ensure that a considerate, meaningful consensus is obtained?

My last point deals with lupus in the elderly. There is evidence that lupus presentation and disease course is different in elderly patients, and it is possible that life expectation and the frequent co-morbidities and poly pharmacy often seen in the elderly alter the balance of benefits and harms for some recommendations.

I sincerely hope that the guideline team is able to consider these points thoughtfully and thoroughly.

Sincerely,
Jaime Guzman, MD MSc FRCPC
Staff Rheumatologist and Clinical Associate Professor
University of British Columbia

- Name: Kathleen Arntsen
- Institution: Lupus and Allied Diseass Association, Inc.
- Position: Volunteer President & CEO
- Disclosure (optional): Lupus and Allied Diseases Association, Inc. is an all-volunteer 501(c)(3) non-profit organization that receives program funding from individuals, foundations, government entities, associations, and corporations, including health related organizations. As a patient-led organization, our viewpoints are solely based on our own perspectives.

Comment:
Lupus and Allied Diseases Association, Inc. (LADA) is thrilled that the American College of Rheumatology (ACR) is seeking public input on the Project Plan to update the Lupus Guidelines and appreciates the opportunity to provide comments. We commend you for including both people with lupus on the voting panel (page 5, line 128) and a separately convened patient panel (page 5, lines 137-139) to provide unique patient perspectives to inform the voting panel.

We recommend that your process to choose these patient panelists includes individuals that truly represent the diversity of the United States lupus patient population by race, ethnicity, type of lupus, years diagnosed, age, gender, geographic location, knowledge of lupus, and whether currently being treated by a lupus specialist.

As a national patient-led organization, we know firsthand the daily struggles of managing our lupus as well as the challenges that our physicians face in making the best treatment decisions for us. Many of us have experienced horrendous side effects and even permanent harm such as infertility from the treatments we have been prescribed for our lupus and co-morbid conditions.

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It is extremely difficult to be diagnosed correctly with lupus and then due to our healthcare system to have access to a specialist that has the time to work with us to find the right treatment. Since no two lupus patients are alike, a treatment that works in one person may not work in another. Often clinicians are left with a try and fail approach in seeking the most optimal treatment while patients become sicker, organ damage accrues and both patient and physician become more frustrated.

Due to the heterogeneity of both lupus and the patient population, unpredictable relapsing and remitting course of the symptoms, lack of validated biomarkers, clinical endpoints and outcome measures, uniform control group, and existence of background medications—usually immunosuppressants, it has been challenging to develop new treatments in lupus. Lupus is a disease of great unmet need.

In addition, clinical research trials have not been traditionally designed to measure what is most important to those who are participating such as improved daily quality of life, reduction in current drug regimen, side effect tolerability, and co-morbid conditions. Patients are also concerned with potential cosmetic side effects such as hair loss, rashes, weight gain, gastrointestinal problems; things that may be socially challenging to young people in the prime of their life.

Until all lupus clinical research focuses on the goals of controlling symptoms, preventing complications, limiting organ damage, increasing survival, and improving overall patient health and daily functioning, and people with lupus can be tested for pharmacogenomics and precision medicine is the standard for care, it becomes the responsibility of organizations like the ACR to establish reasonable guidelines that will allow clinicians the ability to prescribe treatments in the best interest of that individual patient.

Therefore, we strongly encourage you to consider allowing lupus clinicians the flexibility to prescribe the most appropriate treatment based on both the drug including its mechanism of action, mechanism of delivery (oral, injectable, infusible), whether brand vs. generic, biologic vs. biosimilar, innovative vs. traditional; and an individuals' past personal and family medical history, adverse event record, concomitant medications, and ability to adhere due to treatment regimen, side effects, insurance coverage, affordability and accessibility.

The lupus community has eagerly awaited the arrival of newer, efficacious drugs and all of us here at LADA are excited that innovative drugs have been recently approved and that there are a multitude of treatments for lupus nephritis and lupus currently in the development pipeline. The ACR's Project Plan to update the Lupus Guidelines will be an important step during this critical juncture of lupus drug discovery, development and delivery.

Thank you again for the opportunity to provide our exclusive patient viewpoints and for recognizing the value of including people with lupus in the process.

- Name: Grant Louis
- Institution: Arthritis and Rheumatism Associates, P.C.
- Position: Rheumatologist

- Disclosure (optional): Nothing to disclose.

Comment:
*If management of major and/or frequent gastrointestinal manifestations of SLE are not included in this set of guidelines, I suggest noting this.

*Should lupus myopathies, even if not addressed, be mentioned?

*Constitutional/Type 2 lupus symptoms such as fatigue, headaches, and insomnia are common complaints in the stable lupus patient without signs of active Type 1 features. Not addressing these concerns in this paper is a missed opportunity, given the importance of these to lupus patients. Perhaps in a future set of SLE guidelines?

*Line 401, page 15, last row of the table: Should low dose steroid be < 0.5 mg/kg to remain consistent?

*Line 659, Should PICO question 20 state something along the lines of co-management of LN between nephrology and rheumatology vs nephrology alone? The assumption is that the SLE patient with LN will likely be followed by rheumatology.

*Line 693, PICO question 22, Rather than use preemptive, consider asking if outcomes of renal transplantation differ at various stages of CKD (e.g. 3a/b vs 4 vs 5).

- Name: Michael George
- Institution: University of Pennsylvania
- Position: Assistant Professor, ACR Guideline Subcommittee Chair
- Disclosure (optional): Yes, I wish to disclose information. Research contract with GSK, BI, and Janssen; consulting fees from AbbVie

Comment:
Approve. Congratulations on fantastic work with a very challenging topic and broad potential scope! Please consider all of the comments here as suggestions to consider. In fact, I imagine you have already considered most if not all of these things.
P4 – Are all of these different situations (no improvement in proteinuria, no improvement in renal function, no improvement in hematuria)? Are there clear definitions for each (in addition to the definitions CRR and PRR that I know are already included)?

P7 – The subgroups here seem to suggest the potential for race-based treatment recommendations. Is this a concern given substantial genetic/ancestry and disease heterogeneity between individuals within racial groups?

P8 (and p10). This is labeled as “subsequent treatment” (as opposed to “initial therapy”) but I was not sure how long “initial therapy” would be – is this a full induction regimen? Is “subsequent therapy”

actually maintenance therapy after induction and if so should this be restricted to patients with response to induction therapy?

P11: Which of these comparators are relevant seems like it might depend in some cases on what the initial therapy was – is that true? Would this eventually contribute to a flow diagram that notes different potential initial therapies followed by different potential therapies to use if there is inadequate response? It may be worth sketching the potential diagram to make sure all of the appropriate comparators are included. It does seem like many somewhat assume that the patient is on MMF. Should there be a comparator of switch to MMF vs. continue cyclophosphamide for those on CYC for initial therapy? What about for patients whose initial regimen is MMF + CNI or MMF + voclosporin – should switch to the other vs. continue the same therapy be a comparator? Or switch to CYC?

P16 and 17 may be very hard to get clear data for – I wonder if it is worth the time doing the literature review for these or if there should just be some general guidance about monitoring these things rather than official guidelines – will defer to the core team. I similarly think P20 could be answered as guidance without a clear evidence-based guideline.

P19: Is there a reason that different in HD vs. PD outcomes would be different in SLE or can this be drawn from renal guidelines?

P27: Should dapsone be included as an intervention

P28: Does stable SLE mean that they are in remission or low disease activity? I'm a bit unclear the difference between P28 and P31.

P37: What defines leukopenia? Does specific neutrophil or lymphocyte count matter? Discussion might note some genetic determinants of leukopenia as well.

For some of the disease manifestation specific treatments, the comparator is sometimes just GC alone or in some severe manifestations could also be GC + CYC. This may limited ability to prioritize between the different interventions – that may be appropriate based on the scope of this guideline, but wanted to make sure this had been considered. I'm imaging a table where columns are different disease manifestations and possible treatments are the rows and there are check boxes for recommended therapies for each disease manifestation. One note - if CYC is the default comparator, does it matter if the patient has had substantial prior CYC exposure?

P59. Seems perhaps lower priority than some of the other recommendations if you are looking to trim. If keeping, is this limited to patients without obvious active arthritis on exam?

P60. Might also consider methotrexate as a comparator vs. the listed interventions

P63. As in some of the above disease-manifestation specific questions it seems likely a voting panel would recommend any of the interventions over just continuing the HCQ/steroid that the patient is on. Should there be an alternative comparator?

P64. Having no therapy or HCQ as the only comparators seems possibly problematic (especially with HCQ perhaps with some contraindication in this situation with cardiomyopathy) – again likely panel would vote for all interventions.

- Name: Bryant England
- Institution: UNMC
- Position: Assoc Prof Medicine, ACR Guideline Subcommittee member
- Disclosure (optional): Nothing to disclose

Comment:
Approve

- Name: Reza Mirza
- Institution: McMaster University
- Position: Academic Rheumatologist
- Disclosure (optional): Nothing to disclose

Comment:
Approve

I think there's a good breadth of clinically relevant questions. In particular, I think their approach to PICO questions with many possible interventions/comparators was efficient.

- Name: Sheila Angeles-Han
- Institution: CCHMC
- Position: Pediatric rheumatologist
- Disclosure (optional): Nothing to disclose

Comment:
Approve.
May want to consider adding regular ophthalmic screening for patients on hydroxychloroquine as part of care.

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- Name: Jennifer Barton
- Institution: OHSU/VA Portland Health Care System
- Position: Professor of Medicine/Rheumatology Section Chief
- Disclosure (optional): Nothing to disclose

Comment:
Approve. Whenever possible would focus on disparities/variation in response and/or outcome measurement throughout the guideline.

- Name: Elana Bernstein
- Institution: Columbia University
- Position: Florence Irving Associate Professor of Medicine
- Disclosure (optional): Nothing to disclose

Comment:
I approve.

- Name: Christine D. Sharkey
- Institution: UW Madison SMPH
- Position: Clinical Associate Professor, Rheumatologist
- Disclosure (optional): Nothing to disclose

Comment:
I agree with current guidelines. Given lupus is a heterogenous disease I hope guidelines focus in on specifics in certain demographics. I think that defining renal disease will be something to be careful about too. Use of Cr and how to apply that to different demographics.

- Name: Elaine Husni
- Institution: Cleveland Clinic
- Position: Rheumatologist
- Disclosure (optional): Nothing to disclose

Comment:
Agree with the ACR Lupus guidelines as planned.

- Name: Namrata Singh

- Institution: University of Washington Medicine
- Position: MD
- Disclosure (optional): Nothing to disclose

Comment:
Approve

- Name: Marcy Bolster
- Institution: Massachusetts General Hospital
- Position: Director, Rheumatology Fellowship Training Program
- Disclosure (optional): Nothing to disclose

Comment:
The project plan is incredibly well thought out. It is comprehensive, thorough, and actionable. The only comment I have is to be consistent with the PICO question wording of either "Patients with SLE" or "People with SLE" rather than SLE patients.

- Name: Donald Thomas
- Institution: Arthritis and Pain Associates of Prince George's County
- Position: Rheumatologist
- Disclosure (optional): I used to speak for Exagen, but have not done so since 2022. I have no financial ties with them, but wanted to bring this up since I do mention CB-CAPS I speak for GSK and AstraZeneca but this has nothing to do with my comments

Comment:
Page 62, line 2122: The guidelines should recommend that trough, whole blood hydroxychloroquine drug levels be measured irregularly to help with adherence. (this clearly improves disease activity, patient outcomes, and a recent study showed that doing this helps reduce healthcare disparities and is cost effective.

Though we can all argue about what should be the therapeutic goal level, Garg et al does a very nice job summarizing the literature on various drug levels and their associations and finally recommending a level of 750 - 1200 ng/mL. This range encompasses the levels that most of us would agree upon. Although the evidence is weak (no RCTs), there are enough observational studies, and there is a world of practical use and experience by many of us (to include many who are on the guidelines committee) where we have seen the positive results in so many of our patients compared: better disease control,

markedly better adherence (they know we are watching them and they want to please their doctor and this ends up getting them better with their lupus when they take their HCQ).

I'll be elated if this is added. The EULAR guidelines made a huge mistake in not including them. EULAR has really been ahead of the ACR thus far with lupus management guidelines... but this could be one area of overtrumping them (you also have many other wonderful assessments in the outline and I look forward to the final product.

NOTE: You should also include assessing the use of EC4d and BC4d (CB-CAPS) with their superior sensitivity and specificity. I do not see them anywhere (so there is no line/'page to give). The amount of literature showing their utility is a lot. How much proof does one need? Also, anti-C1q should be assessed in regards to monitoring lupus nephritis.