SUPPLEMENTARY MATERIALS 2 – PICO Questions

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

Presented in two parts, Lupus Nephritis and SLE Treatment Guidelines, with outlines, PICOs (P1 – P65), good practice statements (GPS) and notes for relevant text discussion.

Lupus Nephritis Treatment Guideline: Outline and PICOs
Brief Outline:

- **A. Introduction to Lupus Nephritis (LN)**
- **B. Renal Biopsy**
- **C. Treatment of LN**
  - **Class II**
  - **Class III / IV (initial and subsequent therapy)**
  - **Class V (initial and subsequent therapy)**
- **D. Therapy for refractory LN**
- **E. Treatment of other lupus-related renal disease**
  - **Lupus podocytopathy**
  - **aPL (+) microangiopathic hemolytic anemia**
- **F. Adjunctive treatments / Considerations for LN patients**
  - **Diet, other medications, infection, vaccines, Mesna, leuprolide**
- **G. Monitoring**
- **H. Renal Replacement Therapy (Dialysis and Transplant)**
- **I. Reproductive Health concerns**
- **J. Pediatric concerns**

A. Introduction to Lupus Nephritis (LN)
Text discussion including definitions of LN, significance of activity and chronicity indices, and definitions of complete renal response (CRR), partial renal response (PRR) and non-response (refractory disease).

B. Renal biopsy:
Good practice statement (GPS): importance of early and ongoing collaboration with nephrology and early biopsy (acknowledging practical limitations)
Text discussion: interpretation of biopsy, importance of biopsy quality; importance of access to care.

Note: the general clinical question is in purple and the PICO question operationalized for the literature search is in blue.

Do all SLE patients suspected of having kidney involvement need a kidney biopsy?

P1. In SLE patients with unexplained proteinuria, hematuria, or impaired kidney function, is knowing the renal histology by biopsy associated with better outcomes than not knowing the renal histology?

Population: Patients with SLE with otherwise unexplained

- Proteinuria alone
- Glomerular hematuria with or without proteinuria with normal kidney function
- Impaired kidney function

Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy
Outcomes:

- Additional or different kidney diagnosis identified (e.g., thrombotic microangiopathic anemia (TMA), acute tubular necrosis (ATN), class change, diabetes mellitus (DM) or arteriosclerosis / arteriolosclerosis.) that impacts decision for and choice of therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Do SLE patients with LN who have achieved at least a partial renal response need a repeat kidney biopsy if a new renal flare is suspected?

P2. In SLE patients with LN who have achieved at least a partial renal response who develop recurrent /worsening proteinuria, hematuria, or impaired kidney function, is knowing the renal histology by biopsy associated with better outcomes than not knowing the renal histology?
Population: LN patients who flare after having achieved a complete or partial renal remission with

- Increased proteinuria alone
- Increased glomerular hematuria with or without proteinuria with stable kidney function
- Worsening kidney function

Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy
Outcomes:

- Additional or different diagnosis identified (e.g., TMA, ATN, class change, medication effect e.g., calcineurin inhibitor (CNI), DM, or arteriosclerosis / arteriolosclerosis), that impacts decision for and choice of therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Should proteinuria level define which patient with SLE has a kidney biopsy?

P3. In SLE patients with fixed (persistent) unexplained proteinuria with or without glomerular hematuria or impaired renal function, is performing a renal biopsy based on the level of proteinuria associated with better outcomes than not basing biopsy on level of proteinuria?
Population: Patients with SLE who have fixed or persistent proteinuria with or without impaired kidney function and with or without glomerular hematuria.

- 200 – 500 mg/day with or without impaired kidney function and with or without glomerular hematuria
- >500 mg/d with or without impaired kidney function and with or without glomerular hematuria

Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy
Outcomes:

- Kidney diagnosis identified (e.g., LN vs TMA, ATN, DM, arteriosclerosis / arteriolosclerosis) that impacts decision for and choice of therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Should an SLE patient with LN undergo a for-cause kidney biopsy during treatment if response is inadequate?

P4. In SLE patients with inadequate response to treatment at ≥ 6 months, is knowing the renal histology from a repeat (for-cause) renal biopsy associated with better outcomes than not knowing the renal histology?

Population: Patients with LN on biopsy being treated with appropriate immunosuppression (including changing / more aggressive therapy) in whom proteinuria does not improve or worsens, and/or kidney function does not improve or worsens and/or glomerular hematuria does not improve or worsens.
Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy
Outcomes:

- Additional or different kidney diagnosis identified on histopathology (e.g., TMA, ATN, class change, medication effect e.g., CNI, DM or arteriosclerosis / arteriolosclerosis) results in a change in therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Should an SLE patient with LN undergo a repeat ("protocol") kidney biopsy during subsequent (maintenance) therapy if they have achieved and maintained a complete or partial renal response?

P5. In SLE patients with LN and complete or partial renal response of at least one year on subsequent (maintenance) therapy (immunosuppressive medication with or without corticosteroids), is knowing the renal histology on a repeat "protocol" biopsy associated with better outcomes than not knowing the renal histology?

Population: Patients with LN diagnosed by a kidney biopsy who have been treated with immunosuppression subsequent (maintenance) therapy, and achieved/ maintained a complete or partial renal response for at least a year

- Complete renal response for at least one year
- Partial renal response for at least one year

Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy
Outcomes:

- Histopathology results in change and/or continuation of therapy
- Histopathology results in withdrawal of therapy (i.e., no activity seen on biopsy)
- Risk of LN flare
- ESKD
- Adverse effects of biopsy.

C. Treatment of Lupus Nephritis

GPS: institution of treatment as soon as possible; importance of comorbidities and extrarenal symptoms in decision making.
Text discussion: evolution of terminology: induction to initial therapy, maintenance to subsequent therapy; steroid monotherapy (including monthly pulse steroid) presented in historical perspective; emerging importance of genetic variants (including APOL-1 and others) and new biomarkers; dosing issues for pediatric patients.
C1. Class II Lupus Nephritis (in absence of lupus podocytopathy)
C2. Class III/IV Lupus Nephritis
C3. Class V Lupus Nephritis

CI. Class II Lupus Nephritis

Does class II LN without lupus podocytopathy require therapy?

P6. In SLE patients with class II LN without lupus podocytopathy on biopsy and without presence of extrarenal SLE activity requiring therapy, does treatment with renin-angiotensin-aldosterone system inhibitors (RAAS-I) and steroid with or without additional immunosuppressive therapy - versus RAAS-I therapy alone - lead to improved outcomes?

Population: SLE patients with class II LN without lupus podocytopathy on renal biopsy with proteinuria or decreased kidney function, without nonrenal SLE activity, and on treatment with RAAS-I with:

- Proteinuria > 0.5 gm
- Glomerular hematuria with proteinuria > 0.5 gm
- Decreased kidney function with proteinuria > 0.5 gm

Interventions:

- RAAS-I with:
    - Corticosteroid therapy only
    - Corticosteroid therapy plus immunosuppressive therapy
    - Corticosteroid therapy plus CNI therapy

Comparator: RAAS-I therapy only
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of flares
- Cumulative corticosteroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

C2. Treatment of class III/ IV Lupus Nephritis

What are the most effective treatment regimens for initial treatment of SLE patients with Class III/IV LN?

P7. In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with "X" compared to treatment with "Y" for initial therapy (detailed in table) associated with improved outcomes?

Populations:

- Active Class III/IV LN
- Active Class III/IV LN with:
    - Concomitant class V: mycophenolate mofetil/mycophenolic acid (MMF/MPA) vs cyclophosphamide (CYC)
    - Cellular crescents / fibrinoid necrosis (MMF/MPA vs CYC)
    - Decreased kidney function (MMF/MPA vs CYC)
    - In African Americans (MMF/MPA dose, CYC vs MMF/MPA, and monthly IV CYC vs Euro-lupus protocol)
    - In Hispanics (MMF/MPA dose and CYC vs MMF/MPA)
    - In Asians (MMF/MPA dose and CYC vs MMF/MPA)
    - Proteinuria < 0.5 gm/d (RAAS-I question only)
    - Proteinuria ≥ 3 gms/24 hours (MMF/MPA + belimumab vs MMF/MPA + voclosporin)

Not all comparisons will be relevant for all patient groups.

Intervention (X)	**Comparator (Y)**
Steroid regimen with other therapies:	
Pulse steroid / mod/high dose (0.5 -1 mg/kg)	Pulse steroid / low dose steroid (<0.5 mg/kg) Mod-high dose steroid (0.5 -1 mg/kg) only
Pulse steroid / low dose (<0.5 mg/kg)	Mod - high dose steroid (0.5 -1 mg/kg) only
RAAS-I (<0.5 gm protein pts only)	No RAAS-I (<0.5 gm protein pts only)
CYC:	
IV monthly CYC (NIH protocol)	Eurolupus CYC

	Oral CYC
Any (IV) CYC	MMF/MPA (mycophenolic acid)
Any (IV) CYC	MMF/MPA + CNI
Any (IV) CYC	CNI alone
Any CYC plus belimumab	CYC alone
Any CYC plus anti-CD20 therapy	CYC alone
MMF/MPA (mycophenolic acid):	
2 gm/d MMF equivalent	3 gm/d MMF equivalent
MMF/MPA (any dose)	CNI alone
MMF/MPA plus belimumab	MMF/MPA alone (any dose)
MMF/MPA plus CNI*	MMF/MPA alone MMF/MPA plus belimumab CYC plus belimumab
MMF plus anti-CD20 therapy	MMF/MPA alone
Anti-CD 20 plus belimumab	Anti-CD 20 therapy alone

***Eliminated specific CNI names –** but will review literature for any differences among CNIs

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- Cumulative steroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

What are the most effective treatment regimens for subsequent treatment of SLE patients with Class III/IV LN?

P8. In SLE patients who have undergone initial therapy for active Class III/IV LN, is treatment with "X" compared to treatment with "Y" for subsequent therapy (detailed in table) associated with improved outcomes?

Populations:

- Class III/IV LN:
    - Complete response at 6-12 months
    - Partial response at 6-12 months
- Class III/IV LN + Class V (only MMF/MPA alone vs MMF/MPA + CNI after either CYC or MMF/MPA initial therapy)
    - Complete response at 6-12 months
    - Partial response at 6-12 months

Not all comparisons will be relevant for all patient groups.

Intervention (X)	**Comparator (Y)**
Steroid regimen with other therapies:	
Steroid tapered to ≤ 5 mg/d at ≤ 6 mo	Steroid tapered to ≤ 5 mg/d at > 6 mo
Steroid tapered to ≤ 10 mg/d at ≤ 6 mo	Steroid tapered to ≤ 10 mg/d at > 6 mo
Following initial therapy monthly IV CYC:	
Quarterly IV monthly CYC (NIH protocol) for two years	MMF/MPA Azathioprine (AZA)
MMF/MPA	AZA
MMF/MPA plus belimumab	MMF/MPA
MMF/MPA plus CNI	MMF/MPA
MMF/MPA plus anti-CD20 therapy (rituximab or obinutuzumab)	MMF/MPA
Following initial MMF/MPA therapy:	
MMF/MPA	AZA
MMF/MPA plus belimumab	MMF/MPA
MMF/MPA plus CNI*	MMF/MPA
MMF/MPA plus anti-CD20 therapy	MMF/MPA
*MMF, AZA or combination rx. 3-5 yrs.	*MMF, AZA or combination rx. <3 yrs.
*MMF, AZA or combination rx. >5 yrs.	*MMF, AZA or combination rx. 3-5yr

*Time here reflects total duration of LN therapy

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- Cumulative steroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

C3. Treatment of class V Lupus Nephritis

What are the most effective treatment regimens for initial treatment of SLE patients with Class V LN?

P9. In SLE patients with active, newly diagnosed or flare of Class V LN, is treatment with" X" compared to treatment with "Y" for initial therapy (detailed in table) associated with improved outcomes?

Populations:

- Active Class V LN with:
  - Proteinuria < 0.5 gm/d (RAAS-I question only)
  - Proteinuria < 1 gm/d (steroid/immunosuppressive therapy vs no therapy only)
  - Proteinuria ≥ 1 gm/d
  - Proteinuria ≥ 3.5 gm

Intervention (X)	**Comparator (Y)**
Therapy for proteinuria < 0.5 gm/day	
RAAS-I	No RAAS-I
Therapy for proteinuria < 1 gm/day	
Any steroid and/or immunosuppressive therapy	No steroid and/or immunosuppressive therapy
Therapy for proteinuria ≥ 1 gm/day and for ≥ 3.5 gm/day:	
Corticosteroid monotherapy	
Pulse steroid / mod/high dose	No steroid/immunosuppressive therapy Pulse / low dose steroid (<0.5 mg/kg) Mod/high dose steroid (0.5 - 1 mg/kg)

Mod/high dose steroid (0.5 - 1 mg/kg)	No steroid/immunosuppressive therapy
Corticosteroid regimen with other therapies:	
Pulse steroid / mod/high dose (0.5 - 1 mg/kg)	Pulse steroid / low dose steroid (<0.5 mg/kg mg) Mod-high dose steroid (0.5 -1 mg/kg) only
Pulse steroid / low dose (≤25 mg)	Mod - high dose steroid (0.5 -1 mg/kg) only
CNI:	
CNI	No CNI
CYC:	
IV monthly CYC (NIH protocol)	Eurolupus CYC Oral CYC
Any (IV) CYC	MMF/MPA (mycophenolic acid)
Any CYC plus belimumab	CYC alone
Any CYC plus anti-CD20 therapy	CYC alone
MMF/MPA (mycophenolic acid):	
2 gm/d MMF equivalent	3 gm/d MMF equivalent
MMF/MPA plus belimumab	MMF/MPA alone (any dose)
MMF/MPA plus CNI*	MMF/MPA alone MMF/MPA plus belimumab CYC plus belimumab
MMF plus anti-CD20 therapy	MMF/MPA alone
MMF plus any CNI plus belimumab	MMF/MPA alone
Anti-CD 20 plus belimumab	Anti-CD 20 therapy alone

Any belimumab-containing regimen	MMF/MPA plus CNI
For proteinuria > 3.5 gm/d and/or albumin level of 2.0 g/dL: Anticoagulation	 No anticoagulation

***Eliminated specific CNI names –** but will review literature for any differences among CNIs

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of flares
- Cumulative steroid dose
- Treatment related adverse effects including infection
- Thromboembolic events (for anticoagulation intervention only)
- ESKD (dialysis or transplant)

What are the most effective treatment regimens for subsequent treatment of SLE patients with Class V LN?

P10. In SLE patients who have undergone initial therapy for active Class V LN, is treatment with X compared to treatment with Y for subsequent therapy (detailed in table) associated with improved outcomes?

Population:

- Patients with Class V LN and
    - Complete response at 6-12 months
    - Partial response at 6-12 months

Intervention (X)	**Comparator (Y)**
Corticosteroid regimen with other therapies:	
Steroid tapered to ≤ 5 mg/d at ≤ 6 mo	Steroid tapered to ≤ 5 mg/d at > 6 mo
Steroid tapered to ≤ 10 mg/d at ≤ 6 mo	Steroid tapered to ≤ 10 mg/d at > 6 mo
Following initial therapy monthly IV CYC:	
Quarterly IV monthly CYC (NIH protocol) for two years	MMF/MPA AZA

MMF/MPA	AZA
MMF/MPA plus belimumab	MMF/MPA
MMF/MPA plus CNI (any)	MMF/MPA
MMF/MPA plus anti-CD 20 therapy	MMF/MPA
Following initial MMF/MPA therapy:	
MMF/MPA	AZA
MMF/MPA plus belimumab	MMF/MPA
MMF/MPA plus CNI (any)	MMF/MPA
MMF/MPA plus anti-CD 20 therapy	MMF/MPA
*MMF, AZA or combination rx. 3- 5 yrs.	*MMF, AZA or combination rx. <3 yrs.
*MMF, AZA or combination rx. >5 yrs.	*MMF, AZA or combination rx. 3-5yr

***Time here reflects <u>total duration</u> of LN therapy**

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of flares
- Cumulative steroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

D. Therapy for Refractory Lupus Nephritis

Text to define inadequate response / refractory disease and discuss emerging therapies for the future.

How should LN be treated if it has not responded to adequate initial therapy?

P11. If a LN patient has received adequate/appropriate standard treatment for active LN of any class and has not achieved at least a partial renal response (PRR) to that treatment by 6 months, is treatment with "X" compared to treatment with "Y" (detailed in table) associated with improved outcomes?

Population: LN patients being treated for active LN of any class who have been treated with adequate and appropriate standard therapy and who have been adherent to that therapy but have failed to achieve at least a partial renal response after 6 months of treatment.

Intervention (X)	Comparator (Y)
Corticosteroid therapy	
Pulse therapy	No pulse therapy
Increase to high dose oral GC therapy	No increase
Pulse steroid / low dose (<0.5 mg/kg)	Mod - high dose steroid (0.5 -1 mg/kg) only
CYC:	
Change to any (IV) CYC	Continue MMF/MPA
IV CYC plus belimumab	CYC alone
IV CYC plus anti-CD20 therapy	CYC alone
MMF/MPA:	
Increase to 3 gm/d MMF equivalent	Continue 2 gm/d MMF equivalent
MMF/MPA plus belimumab	MMF/MPA alone (any dose)
MMF/MPA plus CNI*	MMF/MPA alone
MMF plus anti-CD20 therapy	MMF/MPA alone
MMF plus any CNI plus belimumab	MMF/MPA alone MMF/MPA plus CNI MMF/MPA plus belimumab
Anti-CD 20 plus belimumab	Anti-CD 20 therapy alone
Any belimumab-containing regimen	MMF/MPA plus CNI
IVIG + any standard therapy	Any standard therapy without IVIG
Leflunomide + any standard therapy	Any standard therapy without leflunomide

***Eliminated specific CNI names –** but will review literature for any differences among CNIs

Outcomes:

- Reduction of proteinuria
- CRR
- PRR

- Preservation of kidney function
- LN Flare rate
- Cumulative steroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

P12. If a LN patient has received adequate/appropriate initial treatment for active LN of any class and did not achieve at least a partial renal response to that treatment after 6 months*, and then received an alternative standard treatment regimen and did not achieve at least a partial renal response after 6 months* (so now considered to have refractory LN), is treatment with "X" compared to treatment with "Y" (detailed in table) associated with improved outcomes?

***Unless progressive worsening (increased proteinuria or decreasing eGFR) over that 6-month period.**

Need to give enough time to see a response and at the same time be aware of letting time pass with a potentially ineffective treatment; will make very clear in the discussion that if patient is getting worse during those 6 months (increasing UPCR or decreasing eGFR), need to change therapy sooner and not wait the full 6 months.

Population: SLE patients being treated for active LN of any class who have been treated with at least 2 adequate and appropriate standard treatment regimens and who have been adherent to their therapies but have failed to achieve at least a partial renal response after at least 6 months of treatment, and are considered to have refractory LN.

Intervention (X)	**Comparator (Y)**
Pulse methylprednisolone	No pulse glucocorticoids given
Add anti-CD20 therapy	MMF/MPA alone
Add anti-CD20 therapy	CYC alone
Add CNI	MMF/MPA/CYC alone
Add belimumab	MMF/MPA/CYC alone
Add belimumab + CNI	MMF/MPA/CYC alone
Add leflunomide	MMF/MPA/CYC alone
Add IVIG	MMF/MPA/CYC alone
Refer for clinical trial for refractory LN	MMF/MPA/CYC alone

Outcomes:

- Reduction of proteinuria
- CRR

- PRR
- Preservation of kidney function
- LN Flare rate
- Cumulative steroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

E. Treatment of other lupus-related renal disease:
Text discussion: importance of other renal pathology seen in SLE including renovascular disease (arterial or venous), ATN, medication effects e.g., CNI, non-APL related TMA, DM and ASCVD. (Treatment recommendations for these are beyond our scope.)

E1. aPL-positive TMA
Focus on +aPL TMA here but recognize other causes (e.g., complement-mediated TMA, TTP, and others). GPS: suggest early involvement of hematology specialists and collaborative work-up/ therapy.
E2. Lupus podocytopathy (collapsing glomerulopathy)
Text to discuss that Podocytopathy excludes Class V. If no EM, cannot make a diagnosis of podocytopathy – may be a limitation. However, Class II plus significant proteinuria usually indicates podocytopathy (if EM unavailable).

E1. (+) aPL and thrombotic microangiopathy
In SLE patients with +aPL / APS and thrombotic microangiopathy on renal biopsy, does anticoagulation or aPL-directed immunosuppressive therapies improve outcomes compared to not using these therapies?

P13. In SLE patients with (+)aPL / APS and thrombotic microangiopathy on renal biopsy, do anticoagulation or immunosuppressive therapies compared to no additional medication improve clinical outcomes?
Populations:
- SLE patients with (+)aPL or APS and thrombotic microangiopathy on renal biopsy and concomitant lupus nephritis receiving standard immunosuppressive therapy
- SLE patients with (+)aPL or APS and thrombotic microangiopathy on renal biopsy, without concomitant lupus nephritis

Interventions:
- Anticoagulation
- Anticoagulation plus
    - Anti-CD20 therapy
    - Eculizumab / complement inhibition
    - mTOR inhibitor therapy
    - Plasmapheresis

Comparator:
- No aPL-directed therapy (for anticoagulation)
- Anticoagulation alone (for all others)

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Thromboembolism
- Treatment related adverse effects including infection
- Risk of ESKD

E2. Lupus podocytopathy (collapsing glomerulopathy)

In SLE patients with lupus podocytopathy on biopsy who are already on RAAS-I therapy, does adding corticosteroid with or without immunosuppressive therapy improve outcomes?

P14. In SLE patients with changes of lupus podocytopathy (diffuse epithelial cell foot process -podocyte- effacement) on renal biopsy who are on RAAS-I therapy, does steroid with or without immunosuppressive therapy versus RAAS-I alone improve clinical outcomes?

Population: SLE patients with proteinuria > 0.5 gm with or without decreased kidney function, and changes of lupus podocytopathy (diffuse epithelial cell foot process -podocyte- effacement) on renal biopsy

- Proteinuria > 0.5 gm
- Decreased kidney function with proteinuria > 0.5 gm

Interventions:

- RAAS-I with:
    - Steroid therapy (any dose)
    - Steroid therapy plus any immunosuppressive therapy (including MMF, AZA, CYC, CNI)

Comparator: RAAS-I alone

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of flares
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

F. Adjunctive treatments /special considerations for LN patients

GPS/text discussion: Best practices surrounding LN therapy with referral to appropriate guidelines / resources.

Including: infection screening and vaccinations; reproductive health issues; cardiovascular health; bone health; renal dosing for medications; pediatric concerns; treatment with RAAS-I and SGLT2-I (reference KDIGO guideline); use of Mesna with CYC (reference oncology guidelines).

F1. HCQ

Should SLE patients with LN be treated with hydroxychloroquine (HCQ) if not already taking this (and if they have no contraindications)?

P15. In SLE patients with presumed or biopsy-confirmed LN, does initiating HCQ (if not already taking and no contraindications) improve clinical outcomes compared to not taking HCQ?

Population: SLE patients with presumed or biopsy-proven LN who are not on HCQ (and have no contraindication to taking)

Intervention: HCQ
Comparator: No HCQ
Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Cumulative steroid dose
- Risk of flare
- Treatment related adverse effects (retinal and cardiac toxicity)
- ESKD (dialysis or transplant)

G. Monitoring LN activity

Text: discussion of alternative measures including Cystatin C and others.
Review use of more convenient or alternative urine protein tests compared to using a standard 24-hour urine protein collection: reference renal literature / systematic review /guidelines and include limitations of protein-creatinine ratio versus 24 hour collection. (Ex: Kamińska J, et al. Diagnostic utility of protein to creatinine ratio (P/C ratio) in spot urine sample within routine clinical practice. Critical reviews in clinical laboratory sciences. 2020 Jul 3;57(5):345-64.)

How frequently should urine protein be checked in SLE patients, including those with and without LN?

P16. In SLE patients -with or without presumed or biopsy proven LN – does regularly monitoring urine protein at certain intervals lead to better outcomes than not checking this regularly?

Population: SLE patients

- Without known or suspected nephritis.
- On initial LN therapy
- On subsequent LN therapy
- Who have completed and stopped LN therapy

Intervention: Urine protein testing (any method other than dipstick)

- Every 1 month
- Every 2 months
- Every 3 months
- Every 6 months
- Yearly

Comparator: No regular schedule for urine protein testing
Outcomes:

- Reduction of proteinuria (N/A for no LN hx or those who have had resolution of proteinuria)
- Preservation of kidney function
- LN flare
- Cumulative corticosteroid dose
- ESKD (dialysis or transplant)

How frequently should anti-dsDNA antibody and complement levels be checked in SLE patients with LN?

P17. In SLE patients with presumed or biopsy proven LN does regularly monitoring anti-dsDNA antibody andC3C4 at certain intervals lead to better outcomes than not checking these regularly?

Population: SLE patients

- On initial LN therapy
- On subsequent LN therapy
- Who have completed and stopped LN therapy

Intervention: Anti-ds DNA antibody and complement C3 and C4

- Every 1 month
- Every 2 months
- Every 3 months
- Every 6 months
- Yearly

Comparator: No regular schedule for testing

Outcomes:

- Reduction of proteinuria (if applicable)
- Preservation of kidney function
- LN flare
- Cumulative corticosteroid dose
- ESKD (dialysis or transplant)

H. Renal replacement therapy: Dialysis and transplant

What is the impact of renal transplant on patients with LN and ESKD, compared to dialysis?

P.18 In SLE patients with LN with ESKD, does renal transplantation improve clinical outcomes compared to dialysis?

Population: Patients with LN and ESKD

Intervention: Renal transplantation

Comparison: Hemodialysis or peritoneal dialysis

Outcomes:

- Patient survival
- Incidence of infection
- Incidence of CVD
- Quality of life
- Risk of SLE flare
- Disease damage

Is there a difference in clinical outcomes between SLE patients with ESKD using hemodialysis versus peritoneal dialysis?

P19. In SLE patients with LN and ESKD, does use of hemodialysis impact clinical outcomes compared to peritoneal dialysis?

Population: Patients with LN and ESKD

Intervention: Hemodialysis

Comparator: Peritoneal dialysis

Outcomes:

- Patient survival
- Incidence of infection
- Quality of life
- Risk of SLE flare
- Disease damage

Are outcomes improved for SLE patients on renal replacement therapy if they follow regularly with rheumatology in addition to nephrology?

P20. In SLE patients with LN who require renal replacement therapy (RRT), does regular follow up with rheumatology (in addition to nephrology) impact clinical outcomes compared to not following regularly with rheumatology?

Population: Patients with LN on RRT

- On dialysis
- S/p renal transplantation

Intervention: Regular rheumatology follow up
Comparator: No regular rheumatology follow up
Outcomes:

- Patient survival
- Quality of life
- SLE flare
- Hospitalization
- Disease damage

In SLE patients who have undergone renal transplantation does taking/ continuing HCQ following transplantation improve clinical outcomes?

P21. In SLE patients with LN status who are status post renal transplantation, does taking HCQ post-transplant improve clinical outcomes compared to not taking it?

Population: SLE patients with LN s/p renal transplantation
Intervention: HCQ
Comparator: No HCQ
Outcomes:

- Patient survival
- Quality of life
- SLE flare
- Hospitalization
- Disease damage

In SLE patients approaching ESKD, does preemptive renal transplant improve clinical outcomes?

P22. In SLE patients with LN at risk of developing ESKD, does preemptive renal transplant improve clinical outcomes compared to initiating dialysis and no preemptive transplant?
Population: SLE patients with lupus nephritis (LN) at risk of developing ESKD
Intervention: Preemptive renal transplant
Comparator: No preemptive transplant and dialysis
Outcomes:

- Graft survival
- Mortality
- Quality of life
- SLE flare
- Hospitalization

Does high lupus disease activity at the time of renal transplant impact clinical outcomes?

P23. In SLE patients with LN and ESKD, does delaying transplant until clinical or serologic remission, compared to not delaying transplant, impact outcomes?

Population: SLE patients with lupus nephritis (LN) and ESKD
Intervention:

- Transplant with clinical disease activity
- Transplant with serologic activity only

Comparator:

- Transplant with SLE in clinical and serologic remission

Outcomes:

- Graft survival
- Mortality
- Recurrent SLE nephritis in graft

Does addition of anticoagulation improve outcomes in SLE patients with +aPL or APS who are undergoing renal transplant?

P24. In SLE patients s/p renal transplant due to LN and who have +aPL or APS, does anticoagulation with warfarin, compared to no anticoagulation, result in improved outcomes?
Population: Patients who had a renal transplant due to LN with aPL or APS
Intervention: anticoagulation with warfarin
Comparator: no anticoagulation
Outcomes:

- Graft survival
- Mortality
- Vascular (thromboembolic) events
- Bleeding

Does addition of aPL-directed immunosuppressive therapy improve outcomes in SLE patients with +aPL or APS who are undergoing renal transplant?

P25. In patients who had a renal transplant due to LN and who have +aPL or APS, does aPL-directed immunosuppression result in improved outcomes compared to standard of care?
Population: Patients who had a renal transplant due to LN with +aPL or APS
Intervention: immunosuppression (pre and/or post)

- Sirolimus
- Eculizumab
- Anti-CD20 therapy
- Belatacept
- IVIG

Comparison: standard of care
Outcomes:

- Graft survival
- Mortality
- Vascular (thromboembolic) events
- Adverse effects of treatment (bleeding or infection)

SLE Treatment Guideline Outline and PICOs:

A. Diagnosis and Monitoring
B. Comorbidities and risk management (discussion/referral to guidelines/references)

- **Bone health (osteoporosis and avascular necrosis)**
- **CVD risk**
- **Lifestyle (smoking / vaping, diet)**
- **Psychiatric issues**
- **Cancer screening (cervical cancer screening)**
- **Infection risk (vaccines, screening for latent infection e.g., hepatitis B, C and TB, PJP prophylaxis)**
- **Fibromyalgia / central pain syndrome / type 2 SLE (text discussion – beyond scope of this GL)**

C. Medications: risks / special considerations
D. Treatment: guiding principles

- **Goals**
- **Remission/ LDA**

E. Medical management by organ system

- **Constitutional**
- **Hematologic**
- **Neuropsychiatric**
- **Cutaneous/ mucocutaneous**
- **Serositis**
- **Musculoskeletal**
- **Vasculitis**
- **Cardiopulmonary**
- **Renal – Lupus Nephritis GL**
- **Reproductive health**
- **APS: important component of SLE manifestations, beyond the scope of this GL**

F. Non-pharmacologic treatments

A. Diagnosis and Monitoring
GPS: clinical and serologic testing for diagnosis and monitoring of SLE, importance of early diagnosis.
Text discussion addressing issues of access to care, healthcare disparities, utility of classification criteria in clinical care.
Refer to ACR's Quality Measures for SLE:
(https://acrjournals.onlinelibrary.wiley.com/doi/epdf/10.1002/acr.25143)

Does regular use of activity and damage measures improve clinical outcomes for patients with SLE?

P26. In patients with SLE, does use of regular assessment instruments versus not using these instruments impact clinical outcomes?
Population: Patients with SLE
Intervention:
- Disease activity measure at each visit
- Disease damage measure yearly

Comparator: No measures at visits
Outcomes:
- Flare rate
- Disease damage
- Mortality
- Comorbidities
- Quality of life

B. Comorbidities and risk management: GPS and text discussion for most topics here.
B1. Bone health:
Glucocorticoid induced osteoporosis: refer to ACR glucocorticoid-induced osteoporosis guideline (GIOP GL); refer to standard GL for other patients.
Avascular necrosis: Text discussion: importance of risk reduction, screening and referral to/ collaboration with orthopedics and metabolic bone specialists.

B2. Cardiovascular / Metabolic: screening and therapy
GPS regarding increased risk of CVD and necessity of appropriate screening and referral for therapy. Risk factor assessment and modification as responsibilities of the patient's care team, including the primary care physician and/or a preventive cardiologist. Consistent with the 2019 ACC/AHA primary prevention guidelines for the general population, all individuals with SLE between 20-75 years of age should be assessed for traditional risk factors for atherosclerotic cardiovascular disease including hypertension, cigarette smoking, diabetes mellitus, dyslipidemia, and obesity. In addition, all patients should be assessed for "risk-enhancing factors" as defined by the 2018 AHA/ACC guideline on the management of blood cholesterol. Patients should then undergo risk assessment for ASCVD using a risk calculator.

B3. Lifestyle factors
Photoprotection, cessation of smoking and/or vaping, dietary modifications: GPS/Text discussion**B4. Psychiatric comorbidity:**
GPS/ text discussion regarding importance of regular assessment and appropriate referral.

B5. Routine cancer screening
GPS regarding general cancer screening as per general population with exception of cervical cancer screening (text discussion). Systematic reviews on cancer screening specifically for patients with SLE: studies concur that general population screening measures, especially for cervical cancer, are necessary in SLE patients.
Cervical cancer screening: Refer to consensus statement in Guidelines for Cervical Cancer Screening in Immunosuppressed Women Without HIV Infection. Moscicki AB, et al. J Low Genit Tract Dis. 2019;23(2):87.

B6. Infection risk:
Vaccines:
Refer to ACR Vaccine GL, add in comments regarding ACR guidance on Covid vaccines, mention RSV as new option. Pediatric concerns to be included.

Screening for latent infection:
Hepatitis B and Hepatitis C: Follow CDC recommendations**.**
Screening for latent TB: GPS / text discusion, refer to available guidelines
PJP prophylaxis:
When is PJP prophylaxis indicated for patients with SLE on steroid or immunosuppressive therapy?

P27. In patients with SLE for whom immunosuppressive therapy is planned, does prophylactic treatment for PJP reduce risk of infection compared to no prophylactic treatment?

Population: SLE patients for whom immunosuppressive therapy is planned

- With underlying lung disease
- Without underlying lung disease

- Immunosuppressive therapies:
  - Corticosteroid (prednisone $\geq$ 20 mg/day for $\geq$ 4 weeks)
  - Methotrexate
  - Azathioprine
  - MMF/MPA
  - CNIs
  - CYC
  - Anti-CD20 inhibitors
  - Belimumab

- Anifrolumab

Intervention:

- Prophylaxis for PJP
  - Bactrim
  - Atovoquone

Comparator:

- No PJP prophylaxis

Outcomes:

- PJP infection
- Adverse effects of PJP prophylaxis therapy: for Bactrim, rash and allergy; for atovoquone, GI effects and headache.

B7. Non-inflammatory manifestations:
GPS / text discussion: Central sensitization syndromes / fibromyalgia / Type 2 SLE are important determinants of quality of life for SLE patients, but treatment recommendations are beyond our scope.

B8. Pediatric considerations (text discussion as appropriate)

C. Medications: Overview and special considerations
Text discussion and table with relevant dosing concerns / special considerations/ corticosteroid tapering, and pediatric dosing. Lupus-related notes on safe use, adverse effects, specifics for screening /monitoring. Include NSAIDs, corticosteroids, antimalarials, Immunosuppressants, biologics.
Glucocorticoid GPS: The damage from steroids is well documented, emphasize least dose for shortest time as a rule.

In stable SLE patients, does lowering baseline prednisone dose improve clinical outcomes and reduce adverse medication effects compared to maintaining a dose of 10 mg daily?

P28. In patients with stable SLE, what is the impact of lowering prednisone to 2.5, 5 or 7.5 mg daily on clinical outcomes and adverse effects compared to maintaining prednisone 10 mg daily?
Population: Patients with stable SLE on daily prednisone
Intervention: Prednisone daily dose (or equivalent), maintenance (> 6 months)

- 2.5 mg/d
- 5 mg/d
- 7.5 mg/d

Comparator: Prednisone 10 mg/day > 6 months
Outcomes:

- Osteoporosis

- Hypertension
- Fractures
- Cataracts
- T2DM
- Infections
- SDI (disease damage)
- Quality of Life

Does treating SLE patients with an organ-threatening disease flare with pulse steroid followed by oral prednisone taper improve clinical outcomes and reduce adverse medication effects compared to treating with an oral prednisone taper alone?

P29. In patients with organ- threatening SLE, what is the impact of pulse methylprednisolone (250-1000 mg) followed by prednisone taper compared to prednisone taper only on clinical outcomes and adverse medication effects?
Population: Patients with organ threatening SLE flare
Intervention: Pulse therapy (250-1000 mg IV for 1-3 days) followed by prednisone taper
Comparator: Oral prednisone taper only
Outcomes:

- Flare
- Osteoporosis
- Hypertension
- Fractures
- Cataracts
- T2DM
- Infections
- SDI (disease damage)
- Quality of Life

In SLE patients with active SLE (newly diagnosed or flare) being treated with HCQ and prednisone ≥ 20 mg daily for > 4 weeks, does initiating immunosuppressive therapy with a steroid taper result in better clinical outcomes and fewer adverse medication effects?

P30. In patients with active SLE (newly diagnosed or flare) on treatment with HCQ and prednisone ≥ 20 mg daily for > 4 weeks, does initiating immunosuppressive therapy result in better clinical outcomes and fewer adverse medication effects compared to continuing HCQ and prednisone alone at 6 months – 12 months?
Population: Patients with active SLE, newly diagnosed or flare, on HCQ and prednisone ≥ 20 mg for > 4 weeks
Intervention: Initiation of immunosuppression and corticosteroid taper
Comparator: continuing HCQ and prednisone
Outcomes (at 6-12 months):

- Reaching prednisone ≤ 5mg/day
- Stopping GC
- SLE disease activity
- SDI (disease damage)

- Adverse medication effects (infection, cytopenias, diabetes)
- Quality of Life

In SLE patients being treated with HCQ and ≥ 6 months prednisone (> 7.5 mg daily), does initiating immunosuppressive therapy with a steroid taper result in better clinical outcomes and fewer adverse medication effects?

P31. In patients with SLE treated with HCQ and persistent (≥ six months) use of prednisone >7.5 mg daily, does initiation of immunosuppressive therapy with a steroid taper result in better clinical outcomes and fewer adverse medication effects compared to continuing with HCQ and daily prednisone?

Population: Patients with SLE treated with HCQ and persistent (≥six months) prednisone >7.5 mg daily
Intervention: Initiation of immunosuppressive therapy
Comparator: Continuation of current therapy (HCQ and prednisone > 7.5 mg daily)
Outcomes (6-12 months):

- SLE flare
- Osteoporosis
- Hypertension
- Fractures
- Cataracts
- T2DM
- Infections
- SDI (disease damage)
- Quality of Life

In SLE patients in remission on HCQ and prednisone 5 mg daily, does tapering off prednisone result in better clinical outcomes and fewer adverse medication effects?

P32. In SLE patients in remission on HCQ and prednisone 5 mg daily, does tapering off prednisone result in better clinical outcomes and fewer adverse medication effects than continuing the prednisone 5 mg?

Population: Patients with SLE in remission and on HCQ and prednisone 5 mg/d maintenance
Intervention: Full taper to off
Comparator: Continuing 5 mg/d
Outcomes (6-12 months):

- SLE flare
- Osteoporosis
- Hypertension
- Fractures
- Cataracts
- T2DM
- Infections
- SDI (disease damage)

- Quality of Life
- Adrenal insufficiency

Antimalarials:
Text discussion regarding retinal toxicity: Cite ACR/AAO guidance (Rosenbaum, J; PMIDS:33559327) and cardiac toxicity (QTc prolongation and cardiomyopathy): Cite ACR guidance (Desrnairais J;PMID:34697918)

In patients with SLE, does limiting the dose of HCQ to ≤ 5 mg/kg impact clinical effectiveness?

P33. Does HCQ dose of > 5 mg/kg result in better clinical outcomes and control of flares in patients with SLE compared to a dose of ≤ 5 mg/kg?
Population: Patients with SLE taking HCQ
Intervention: HCQ dose of >5 mg/kg
Comparator: HCQ ≤ 5 mg/kg
Outcomes:
- Disease activity
- Flares
- SDI (damage)
- Retinal toxicity
- Cardiac toxicity (Prolonged QTc and/or myopathy)

In patients with SLE on HCQ, does measurement of blood HCQ levels lead to improved clinical outcomes?

P34. In patients with SLE on HCQ, does measuring HCQ blood levels lead to improved clinical outcomes or fewer adverse medication effects than not measuring levels?
Population: Patients with SLE taking HCQ
Intervention: Checking HCQ (whole blood/serum) levels
Comparator: Not checking levels
Outcomes:
- Adherence
- SLE disease activity
- Flares
- Thrombosis,
- Retinal toxicity
- Cardiac toxicity (Prolonged QTc and/or myopathy)

Dermatologic therapies
Discussion in text, Plan table with important topical medications / steroid classes.
Include pregnancy screening for thalidomide, retinoids.

Immunosuppressive and Biologic therapies
Discussion in text, Table with medications.

Include CYC fertility issues (RHGL), contraception for MMF/MPA, TPMT/ NUDT15 for AZA.

D. Guiding therapy principles

GPS: Aim for remission / low disease activity state to improve clinical outcomes.

Being in remission or LDA (regardless of the definition) is associated with improved outcomes in patients with SLE (Ugarte-Gil MF, et al. Lupus Science & Medicine. 2021 Sep 1;8(1):e000542.)

Text discussion regarding goals of therapy: control disease activity, prevent organ damage, improve long term survival, improve QoL, minimize comorbidities, minimize corticosteroid use, minimize medication toxicity

Importance of adherence issues; guiding principles for pediatrics: Minimize steroid exposure (improve bone health, growth and development, and psychosocial outcomes).

Should HCQ be recommended for every patient with SLE unless a contraindication is present?

P35. In patients with SLE, does routine treatment with HCQ (regardless of other therapies), improve clinical outcomes compared to not treating with HCQ?

Population:

- Patients with SLE

Intervention:

- Treating with HCQ (unless a contraindication)

Comparator: Not treating with HCQ

Outcomes:

- Flare risk
- Disease accrual
- Mortality
- Corticosteroid related adverse effects (osteoporosis, infection, diabetes)
- Retinal toxicity
- Cardiac toxicity (Prolonged QTc and/or myopathy)
- Thrombosis
- Quality of life

Can therapy for SLE be tapered off in patients who have achieved clinical remission or a low disease activity state?

P36. In patients with SLE who have achieved remission or low disease activity, does discontinuation of therapy at a particular time point affect clinical outcomes when compared to continuing therapy?

Population:

- Patients with SLE who have achieved remission
- Patient with SLE who have achieved low disease activity

Intervention:

- Discontinuation of immunosuppressive therapy at (from time of complete remission or low disease activity)
    - One year

    - > One year but ≤ 3 years
    - > 3 years
- Discontinuation of HCQ at (from time of complete remission or low disease activity)
    - ≤ 5 years
    - 5-10 years
    - > 10 years

Comparator: Not discontinuing therapy

Outcomes:

- Flare risk
- Disease accrual
- Mortality
- Corticosteroid related adverse effects of osteoporosis and diabetes
- Immunosuppressive therapy related adverse effects of infection and cytopenias for immunosuppressive therapy
- HCQ related adverse effects of retinal toxicity and cardiac toxicity (prolonged QTc and myopathy) for HCQ therapy
- Quality of life

E. Treatment by organ system / medical management

E1. Constitutional symptoms

GPS / text discussion regarding importance of ruling out endocrine, infectious, oncologic, and psychological causes which would demand alternative therapies.

Stress importance of multifactorial etiology (e.g. Arnaud L, et al. Predictors of fatigue and severe fatigue in a large international cohort of patients with systemic lupus erythematosus and a systematic review of the literature. Rheumatology. 2019 Jun 1;58(6):987-96; del Pino-Sedeño T, et al. Effectiveness of nonpharmacologic interventions for decreasing fatigue in adults with systemic lupus erythematosus: a systematic review. Arthritis Care & Research. 2016 Jan;68(1):141-8.

E2. Hematologic manifestations

Text discussion of life-threatening heme diagnoses such as MAS.

In SLE patients with leukopenia, does treatment with immunosuppressive therapy improve or worsen clinical outcomes compared to no immunosuppressive therapy?

P37. In SLE patients with leukopenia, does adding, changing, or discontinuing immunosuppressive therapy improve clinical outcomes?

Population: SLE patients (may be on HCQ)

- Leukopenia not on immunosuppressive medication.
- Leukopenia on immunosuppressive medication (AZA, MMF/MPA, MTX or biologic therapy)

Intervention:

- For non-immunosuppressed patients: addition of
    - Azathioprine
    - MMF/MPA
    - Glucocorticoid
- For patients on immunosuppressants:
    - Stopping or lowering immunosuppressive therapy

Comparator:

- No treatment (or HCQ alone) (for patients not on immunosuppressive medications)
- Continuing therapy at same dose (for patients on immunosuppressive medications)

Outcomes:

- WBC count (increase, decrease or no change)
- Infection
- Mortality
- Disease damage
- Disease flare

Does chronic asymptomatic thrombocytopenia in patients with SLE require medical therapy?

P38. In SLE patients with thrombocytopenia that is chronic and asymptomatic, does addition of immunosuppressive medication impact clinical outcomes compared to not adding medication?

Population: SLE patients with thrombocytopenia (on HCQ or no therapy) that is chronic and asymptomatic:

- >50,000
- 10,000-50,000
- <10,000

Intervention:

- Glucocorticoid therapy
- Immunosuppressive therapy
- Biologic therapy

Comparator:

- No therapy or HCQ alone

Outcomes:

- Life-threatening bleeds
- Mortality
- Treatment related adverse effects of infection
- Disease damage
- Disease flare

In patients with SLE and acute progressive thrombocytopenia, does treatment with glucocorticoid and immunosuppressive therapy (or surgery) lead to improved clinical outcomes compared to glucocorticoid alone?

P39. In SLE patients with acute and progressive thrombocytopenia on HCQ or no therapy, does addition of immunosuppressive therapy (or surgery) to glucocorticoid therapy lead to improved clinical outcomes compared to glucocorticoid therapy alone?

Populations: SLE patients with thrombocytopenia (on HCQ or no therapy), that is acute, progressive and symptomatic:

- >50,000
- 10,000 – 50,000
- <10,000

Intervention:

- Glucocorticoid therapy (high dose) plus
    - Immunosuppressive therapy
        - AZA
        - MMF/MPA
        - Cyclosporine
    - Anti-CD20 therapy
    - Splenectomy
    - IVIG

Comparator:

- Glucocorticoid therapy

Outcomes:

- Life-threatening bleed
- Mortality
- Treatment related adverse effect of infection
- Disease damage
- Disease flare

In SLE patients with autoimmune hemolytic anemia, does addition of immunosuppressive therapy (or surgery) to glucocorticoid therapy lead to improved clinical outcomes?

P40. In SLE patients with autoimmune hemolytic anemia on HCQ or no therapy, does the addition of immunosuppressive therapy or surgery to glucocorticoid therapy improve clinical outcomes compared to glucocorticoid therapy alone?

Populations: SLE patients with autoimmune hemolytic anemia on HCQ or no therapy

Intervention:

- Glucocorticoid therapy (high dose) plus
    - Immunosuppressive therapy
        - AZA
        - MMF/MPA
        - Cyclosporine
    - Anti-CD 20 therapy
    - Splenectomy
    - IVIG

Comparator: Glucocorticoid therapy alone

Outcomes:

- Mortality
- Disease damage
- Treatment related adverse effect of infection
- Disease flare

E3. Neuropsychiatric manifestations

GPS: Endorse multi-disciplinary approach including co-management with neurology and/or psychiatry for evaluation/ treatment with consideration of the use of non-SLE therapies that are

directed toward the specific manifestation (e.g. anti-seizure therapy, anti-psychotic therapy, therapy for movement disorders, PT/OT, etc.)
Perform thorough evaluation for alternative etiologies of neuropsychiatric symptoms/ signs; Rule out metabolic abnormalities, infection, hypertension, PRES, mimicking immune-mediated diseases such as MS, NMOSD, MOGAD.

What is the most effective therapy for lupus myelitis?

P41. In patients with active, newly diagnosed or flare of lupus myelitis*, what is the impact of the listed medical therapies on clinical outcomes compared to standard therapy of pulse steroid with or without CYC?
*Text to include rational for using this term - we are treating inflammatory (and not purely ischemic) lesions.

Population: SLE patients with active, newly diagnosed or flare of lupus myelitis
Interventions: Pulse IV glucocorticoid followed by high dose glucocorticoid and:

- MMF/MPA
- Anti-CD20 therapy
- Anifrolumab
- CYC + anti-CD20 therapy
- CYC + PLEX (plasmapheresis)
- CYC + IVIG
- CYC + PLEX + IVIG
- CYC + anti-CD20 therapy + PLEX + IVIG
- Antithrombotic regime + immunosuppressive regimen

Comparators:

- Pulse IV glucocorticoid followed by high dose glucocorticoid (no additional immunosuppressive)
- Pulse IV glucocorticoid followed by high dose glucocorticoid and IV CYC.

Outcomes:

- Disease activity
- Disease flares
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for lupus-related optic neuritis?

P42. In patients with active, newly diagnosed or flare of optic neuritis secondary to SLE (not NMO)*, does the addition of immunosuppressive therapy to glucocorticoid lead to improved clinical outcomes compared to glucocorticoid with or without CYC?

*Optic neuritis: 1999 ACR nomenclature refers to this entity as "neuropathy, cranial." For the purposes of our recommendations, we are referring to optic neuritis of inflammatory etiology and NOT optic neuropathy of ischemic etiology.

Population: SLE patients with active, newly diagnosed or flare of optic neuritis
Interventions: Pulse IV corticosteroid followed by high dose corticosteroid and:

- MMF
- Anti-CD20 therapy
- Anifrolumab
- CYC + anti-CD20 therapy
- CYC + PLEX
- CYC + IVIG
- CYC + PLEX + IVIG
- CYC + anti-CD20 therapy + PLEX + IVIG
- Antithrombotic regimen + immunosuppressive regimen

Comparators:

- Pulse IV glucocorticoid followed by high dose glucocorticoid (no additional immunosuppressive)
- Pulse IV glucocorticoid followed by high dose corticosteroid +3IV CYC

Outcomes:

- Disease activity
- Disease flares
- Optic nerve damage
- Vision
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias

What is the most effective therapy for lupus-related seizures (occurring in the absence of stroke) in addition to standard antiseizure therapy?

P43. In patients with active, newly diagnosed or flare of lupus seizure in the absence of stroke, does glucocorticoid therapy with or without immunosuppressive or antithrombotic therapy improve clinical outcomes compared to anti-seizure therapy alone?

Population: SLE patients with active, newly diagnosed or flare of lupus seizure in the absence of stroke
Interventions: Anti-seizure medication and addition of:

- Glucocorticoid therapy
- Glucocorticoid therapy +
    - IV CYC
    - MMF/MPA
    - AZA

    - Anti-CD20 therapy
    - Anifrolumab
    - Belimumab
    - Antithrombotic regimen + immunosuppressive regimen

Comparator:

- Appropriate anti-seizure therapy alone.

Outcomes:

- Seizure activity
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective medical therapy for acute confusional state due to SLE?

P44. In patients with acute confusional state secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

*Note of clarification: per the 1999 ACR nomenclature and case definitions for neuropsychiatric lupus, "acute confusional state" is equivalent to "delirium." Neurologists often use the term "encephalopathy" to describe the same clinical state. No treatment option of anti-thrombotics in acute confusional state because the mechanism of acute confessional state is inflammatory and the issue of anti-thrombotics is usually not relevant. These questions pertain to acute confusional state in the absence of stroke**.**

Population: SLE patients with acute confusional state secondary to active SLE
Interventions: Pulse IV glucocorticoid followed by high dose glucocorticoid and:

- MMF
- Anti-CD20 therapy
- Anti-CD20 therapy + PLEX
- Anifrolumab
- Belimumab
- CYC + anti-CD20 therapy
- CYC + PLEX
- CYC + IVIG
- CYC + PLE + IVIG
- CYC + anti-CD20 therapy + PLEX + IVIG

Comparators:

- Pulse IV glucocorticoid followed by high dose glucocorticoid (no additional immunosuppressive)
- Pulse IV glucocorticoid followed by high dose glucocorticoid + IV CYC

Outcomes:

- Disease activity
- Resolution of acute confusional state

- Neurologic damage
- Mortality
- Improvement in quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for lupus-related psychosis in addition to standard antipsychotic therapy?

P45. In patients with active, newly diagnosed or flare of lupus psychosis in the absence of stroke, does glucocorticoid with or without additional (listed) therapies improve clinical outcomes compared to antipsychotic therapy alone?

Population: SLE patients with active, newly diagnosed or flare of lupus psychosis

Interventions: Antipsychotic therapy and addition of:

- Glucocorticoid therapy alone
- Glucocorticoids plus:
    - IV CYC
    - MMF/MPA
    - AZA
    - Anti-CD20 therapy
    - Anifrolumab
    - Belimumab
    - IVIG

Comparators: Antipsychotic therapy alone

Outcomes:

- Resolution of psychosis
- Prevention of recurrent psychosis
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for active mononeuritis multiplex in patients with SLE?

P46. In patients with active, newly diagnosed or flare of mononeuritis multiplex secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

Population: SLE patients with active, newly diagnosed or flare of mononeuritis multiplex
Interventions: Pulse IV glucocorticoids followed by high dose glucocorticoid and:

- MMF/MPA
- Anti-CD20 therapy
- Anifrolumab
- Belimumab
- CYC + anti-CD20 therapy
- CYC + PLEX
- CYC + IVIG
- CYC + PLE + IVIG
- CYC + anti-CD20 therapy + PLEX + IVIG
- Antithrombotic regimen + immunosuppressive regimen

Comparator:

- Pulse IV glucocorticoid followed by high dose glucocorticoid (no additional immunosuppressive)
- Pulse IV glucocorticoid followed by high dose glucocorticoid + IV CYC

Outcomes:

- Resolution of mononeuritis multiplex
- Prevention of recurrent mononeuritis multiplex
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for polyneuropathy secondary to active SLE? **– eliminate since most severe (mononeuritis) and most common (small fiber) are addressed.**

What is the most effective therapy for small-fiber neuropathy secondary to SLE?

P47. In patients with small-fiber neuropathy secondary to active SLE, does addition of glucocorticoid or immunosuppressive therapy to symptomatic (non-immunosuppressive nerve-directed) therapy improve clinical outcomes compared to symptomatic therapy only?
*Note of clarification: small-fiber neuropathy refers to damage to the small diameter somatic and autonomic unmyelinated C-fibers and/or thinly myelinated A-delta fibers. In conjunction with a neurologist, confirmation of the diagnosis via skin biopsy demonstrating decreased intra-epidermal nerve fiber density is strongly recommended. However, it is important to note that skin biopsies have imperfect sensitivity for the diagnosis. Other diagnostic tests such as QSART testing may also be considered.

Population: Patients with small-fiber neuropathy secondary to active SLE
Interventions:

- Glucocorticoid therapy

- MMF/MPA
- AZA
- Anifrolumab
- IVIG
- Belimumab

Comparator: Non-immunosuppressive, symptomatic, nerve-directed therapy alone
Outcomes:

- Improvement of small-fiber neuropathy
- Prevention of recurrent small-fiber neuropathy
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g. Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for cognitive dysfunction or decline secondary to SLE?

P48. In patients with cognitive dysfunction or decline secondary to active SLE in the absence of stroke, does addition of glucocorticoid or immunosuppressive therapy to cognitive rehabilitation therapy improve clinical outcomes compared to cognitive rehabilitation therapy only?

*Note of clarification: per the 1999 ACR nomenclature and case definitions for neuropsychiatric lupus, cognitive dysfunction is defined as significant deficits in any or all of the following cognitive functions: simple of complex attention, reasoning, executive skills, memory, visual-spatial processing, language, and psychomotor speed. Neuropsychological testing should be performed for documentation of cognitive deficits.
Decreased academic performance/school function can be an informative sign in childhood/adolescence.

Population: Patients with cognitive dysfunction or significant cognitive decline secondary to active SLE.
Interventions: Cognitive therapy and addition of:

- Corticosteroid therapy
- MMF/MPA
- AZA
- Anti-CD20 therapy
- Anifrolumab
- Anti-thrombotic therapy

Comparator: Cognitive rehabilitation therapy
Outcomes:

- Further decline in cognitive ability
- Neurologic damage
- Mortality

- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for ischemic stroke in aPL-negative SLE patients?

P49. In SLE patients with ischemic stroke in the absence of aPL who have received acute stroke-directed therapy and/or procedure-based intervention, does addition of glucocorticoid, immunosuppressive therapy, or anticoagulation to antiplatelet therapy improve clinical outcomes compared to antiplatelet therapy only?

Population: Patients with SLE and ischemic stroke in the absence of aPL who have received acute stroke-directed therapy and/or procedure-based intervention, if indicated.
Interventions:

- Anticoagulation
- Corticosteroid therapy
- MMF/MPA
- AZA

Comparator: Antiplatelet therapy alone
Outcomes:

- Improvement of the stroke
- Prevention of recurrent stroke
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias for steroid and immunosuppressive therapies, bleeding for anticoagulation
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

E4. Cutaneous/ mucocutaneous
Tables for guidance on use of 1) Sunscreens and 2) Topical steroid preparations.
GPS regarding referral to dermatologist; importance of collaboration and early diagnosis (include access of care issues);
GPS regarding education and encouragement for patients on use of sunscreen / photoprotection to reduce risk of rash as well as potential disease flare.

In SLE patients with acute cutaneous lupus despite HCQ and topical steroid therapy, what is the most effective additional therapy for persistent rash?

P50. Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy , compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy
Interventions: Continued HCQ and topical steroid therapy with addition of

- Chloroquine
- Quinacrine
- MTX
- AZA
- MMF/MPA
- Belimumab
- Anifrolumab
- Anti-CD-20 therapy

Comparator:

- HCQ and topical steroid therapy

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications - for immunosuppressives including biologics: infection and cytopenias; for antimalarials: retinal toxicity and cardiac toxicity (prolonged QTc and myopathy).

In SLE patients with subacute or chronic cutaneous lupus despite HCQ and topical steroid therapy, what is the most effective additional therapy for persistent rash?

P51. Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy
Interventions: Continued HCQ and topical steroid therapy and addition of:

- Chloroquine
- Quinacrine
- Dapsone
- Retinoids
- MTX
- AZA
- MMF/MPA
- Thalidomide /Lenalidomide
- Belimumab
- Anifrolumab
- Anti-CD-20 therapy
- JAK-I

Comparators:

- HCQ and topical steroid therapy for Dapsone, Retinoids, MTX, ASA, MMF/MPA
- HCQ, topical steroid therapy and immunosuppressive therapy (with MTX, MMF/MPA or AZA) for thalidomide /lenalidomide, belimumab, anifrolumab, anti-CD-20 therapy and JAK-I

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications for immunosuppressives including biologics and small molecules: infection and cytopenias; for antimalarials: retinal toxicity and cardiac toxicity (prolonged QTc and myopathy); for thalidomide and lenalidomide: neuropathy and GI effects; for retinoids: liver toxicity

In SLE patients with bullous lupus, what is the most effective therapy?

P52. In SLE patients with bullous lupus, what is the impact of listed medical treatments compared to steroids alone on clinical outcomes?

Population: SLE patients with bullous LE

Interventions:

- Dapsone
- Colchicine
- Corticosteroids
- Corticosteroids plus:
    - MTX
    - AZA
    - MMF/MPA
    - Anti-CD-20 therapy

Comparators:

- HCQ (for all except anti-CD 20 therapy)
- Oral glucocorticoids
- Stable background meds (including corticosteroid and immunosuppressive medications) for anti-CD 20 therapy

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications: infection and cytopenias (for corticosteroids and immunosuppressives/ biologics); GI upset with dapsone; cytopenias and GI upset with colchicine

In SLE patients with lupus panniculitis, what is the most effective therapy?

Eliminate – uncommon manifestation.

In SLE patients with chilblains, what is the most effective therapy beyond symptomatic measures?

P53. In SLE patients with chilblains, does addition of the listed medical treatments compared to symptomatic measures (with or without topical therapies) lead to improved clinical outcomes?

Population: SLE patients with chilblains

Interventions: Symptomatic therapy and

- Topical steroid
- Topical calcineurin inhibitors
- HCQ
- Chloroquine
- Dapsone
- Calcium channel blockers
- Retinoids
- MTX
- AZA
- MMF/MPA
- Thalidomide
- Lenalidomide
- Belimumab
- Anifrolumab

Comparators:

- For topical steroid and topical calcineurin inhibitors, no therapy other than gloves/socks/warmers (symptomatic)
- For HCQ and chloroquine: symptomatic therapy, topical steroid therapy and topical calcineurin inhibitors
- For all others: symptomatic therapy, antimalarials, topical steroid therapy and topical calcineurin inhibitors

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications: Adverse impact of medications: retinoids: liver toxicity; immunosuppressives: infection and cytopenias; thalidomide/lenalidomide: neuropathy and GI effects; antimalarial: retinal and cardiac toxicity; dapsone and colchicine: GI effects; calcium channel blockers: lightheadedness.

In SLE patients with cutaneous vasculitis, what is the most effective therapy?

P54. In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population: SLE patients with cutaneous vasculitis
Interventions:

- Topical steroid
- Topical calcineurin inhibitors,
- HCQ
- Chloroquine
- Dapsone
- Colchicine
- Retinoids
- Pentoxyfylline
- MTX
- AZA
- MMF/MPA
- Thalidomide
- Lenalidomide
- Belimumab
- Anifrolumab

Comparators:

- For topical steroid and topical calcineurin inhibitors: no therapy as comparator
- For HCQ and chloroquine: topical steroid therapy and topical calcineurin inhibitors as comparators
- For all others: antimalarials plus topical steroid therapy and topical calcineurin inhibitors
- For Thalidomide, lenalidomide, belimumab and anifrolumab: also compare to antimalarials, topical steroid, topical calcineurin inhibitors and immunosuppressives (MTX, AZA, MMF/MPA)

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications: retinoids: liver toxicity; immunosuppressives including biologics: infection and cytopenias; thalidomide/lenalidomide: neuropathy and GI effects; antimalarial: retinal and cardiac toxicity; dapsone, pentoxifylline, colchicine: GI effects

In SLE patients with focal alopecia due to CLE or SLE, does addition of topical therapies to systemic therapy improve clinical outcomes?

P55. In SLE patients with focal active alopecia due to CLE or SLE, does the addition of topical treatment to systemic therapies, compared to no topical treatment, improve clinical outcomes?

Population: Patients with SLE and focal alopecia on systemic therapy (HCQ and/or immunosuppressives)
Interventions:

- Intralesional Kenalog with systemic treatment
- Intralesional Kenalog alone
- Topical steroid

Comparators:

- Antimalarials
- Immunosuppressives

Outcomes:

- Rate and amount of improvement

In SLE patients with severe oral ulcers, does topical therapy improve clinical outcomes?

P56. In patients with oral ulcers due to SLE does the addition of targeted local therapies to standard systemic therapies, compared to no targeted local therapies, improve clinical outcomes?

Population: Patients with SLE and mouth ulcers on systemic therapy (HCQ and/or immunosuppressives)

Interventions:

- Intralesional Kenalog
- Topical steroids

Comparators:

- Antimalarials
- Immunosuppressives

Outcomes:

- Rate and amount of improvement

E5. Serositis

In SLE patients with pericarditis, what is the most effective therapy?

P57. In SLE patients with pericarditis what is the impact of listed medical therapies or pericardectomy versus baseline therapy alone on clinical outcomes?

Population: Patients with lupus and pericarditis

Intervention:

- NSAIDs
- Colchicine
- Glucocorticoid therapy alone
- Methotrexate
- Azathioprine
- MMF/MPA
- Cyclophosphamide
- Belimumab
- Anifrolumab
- Anti-CD20
- Anti IL-1therapy
- Pericardiectomy

Comparator:

- Hydroxychloroquine and/or NSAIDs
- Colchicine with HCQ (for all but HCQ, NSAID and colchicine)
- HCQ / NSAID / colchicine
- Corticosteroid (for MTX, AZA, MMF/MPA, CYC, biologics and pericardectomy)

Outcomes:

- Resolution of pericarditis
- Prevention of pericarditis flares
- Prevention of pericardiectomy
- Prevention of chronic pericarditis (≥6 mo)
- Improvement in quality of life
- Cumulative GC
- Adverse treatment events: immunosuppressives including biologics, infection and cytopenias; colchicine and NSAIDs: GI symptoms; steroid alone: osteoporosis and infection
- Mortality
- Disease damage

In SLE patients with pleuritic pain and/or pleural effusion, what is the most effective therapy?

P58. In patients with SLE and pleural disease what is the impact of medical therapy versus baseline therapy alone on clinical outcomes?

Population: Patients with lupus and pleural disease (pleuritic pain, effusion)

Intervention:

- NSAIDs
- Colchicine
- Glucocorticoid therapy alone
- Methotrexate
- Azathioprine
- MMF/MPA
- Cyclophosphamide
- Belimumab
- Anifrolumab
- Anti-CD20
- Anti IL-1 therapy

Comparator:

- Hydroxychloroquine and/or NSAIDs
- Colchicine with HCQ (for all but HCQ, NSAID and colchicine)
- HCQ / NSAID / colchicine
- Corticosteroid (for MTX, AZA, MMF/MPA, CYC, biologics)

Outcomes:

- Resolution of pleural disease
- Prevention of pleural disease flares
- Prevention of shrinking lung syndrome

- Prevention of fibrothorax
- Improvement in quality of life
- Cumulative GC
- Adverse treatment events: immunosuppressives including biologics, infection and cytopenias; NSAIDs and colchicine: GI effects; steroid alone: osteoporosis and infection
- Mortality
- Disease Damage

E6. Musculoskeletal

Is there a benefit to imaging symptomatic joints in SLE patients with arthritis?

P59. In patients with SLE and lupus arthritis or tendonitis, does imaging with US or MRI compared to not doing this imaging improve clinical outcomes?
Population: Patients with lupus arthritis or tendonitis
Intervention:
- Ultrasound
- MRI

Comparator: PE alone
Outcomes:
- Diagnosis of subclinical arthritis
- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Disease activity
- SLE flares
- Joint damage
- Disease damage
- Quality of life
- Functional status

In SLE patients with arthritis, what is the most effective therapy?

P60. In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?
Population: SLE patients with active lupus arthritis
Intervention:
- HCQ and other antimalarials (AM)
- NSAIDs
- Glucocorticoid-containing regimens
- Immunosuppressants
    - MTX
    - MMF/MPA
    - AZA
    - Leflunomide
    - CNI
- Biologics

    - Anti-CD20
    - Belimumab
    - Anifrolumab
    - Abatacept

Comparator:

- No treatment (for HCQ and NSAIDs)
- HCQ alone (for all other options)
- HCQ +steroid (for all other options)

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Joint damage
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias; steroids: osteoporosis and infection; NSAIDs: GI side effects; Antimalarials: retinal and cardiac effects (prolonged QTc and myopathy)

In SLE patients with chronic persistent arthritis on HCQ with or without corticosteroid, what is the most effective therapy?

P61. In patients with SLE and chronic persistent lupus arthritis on HCQ and steroid, does treatment with listed medical therapies compared to no added treatment impact clinical outcomes?

Population:

- SLE patients with chronic persistent lupus arthritis on HCQ and steroid
- SLE patients with chronic persistent lupus arthritis on HCQ, steroid and standard immunosuppressives

Intervention:

- Immunosuppressants (for HCQ/steroid group)
    - MTX
    - MMF/MPA
    - AZA
    - Leflunomide
    - CNI
        - CYC
- Biologics (for HCQ/steroid group and for HCQ/steroid/immunosuppressant group)
    - Anti-CD20
    - Belimumab
    - Anifrolumab
    - Abatacept
    - Tocilizumab

- Jak-I (for HCQ/steroid/immunosuppressant group only)

Comparator:

- HCQ and steroids alone
- HCQ, steroid and standard immunosuppressive therapy (for biologics and JAK-I)

Outcomes:

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Joint damage
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias; steroids: osteoporosis and infection; NSAIDs: GI side effects; Antimalarials: retinal and cardiac effects (prolonged QTc and myopathy)

In SLE patients with Jaccoud's arthropathy, does addition of medical therapy to standard of care (PT/OT and/or surgery) improve clinical outcomes?

P62. In SLE patients with chronic Jaccoud's arthropathy, what is the impact of medical therapy or surgery vs PT/OT on clinical outcomes?

Populations: SLE patients with Jaccoud's arthropathy

Interventions:

- Hand arthroplasty
- Immunosuppressive therapy (MMF, AZA, MTX, or other standard immunosuppressives)

Comparator: PT/OT including splinting

Outcomes:

- Function of affected joints (hand function measure)
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Quality of life
- Treatment-related adverse events: infection and cytopenias for immunosuppressive therapies; surgical complications of hand arthroplasty for surgery adverse outcomes

E7. Renal: refer to Lupus Nephritis Guideline

E8. Vasculitis (non-cutaneous)

In SLE patients with (non-cutaneous) vasculitis, what is the most effective therapy?

P63. In patients with SLE with vasculitis (not including cutaneous vasculitis) on HCQ and steroid, what is the impact of adding listed therapies versus not adding additional therapy on clinical outcomes?

Population: SLE patients with vasculitis (not including cutaneous vasculitis) on HCQ/steroid.
Interventions:

- High dose glucocorticoid-containing regimens – pulse followed by high dose
- Immunosuppressants
    - MTX
    - MMF
    - AZA
    - CNI
    - Cytoxan
- Biologics
    - Anti-CD20
    - Belimumab
    - Anifrolumab
- IVIG
- Plasmapheresis

Comparator: HCQ and steroid
Outcomes:

- Vasculitis activity
- Disease activity
- SLE flares
- Disease damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment -related adverse events: steroids: infection and osteoporosis; immunosuppressives including biologics and small molecules: infection and cytopenias; IVIG: headache; plasmapheresis: low blood pressure

E9. Cardiopulmonary
Rarer complications to be noted in text but not addressed in PICOs.

In SLE patients with myocarditis, what is the most effective therapy?

P64. In patients with lupus myocarditis what is the impact of listed therapies vs no therapy or HCQ alone on clinical outcomes?
Population: SLE patients with lupus myocarditis

- Acute and worsening
- Chronic and persistent

Interventions:

- Glucocorticoid-containing regimens
- Immunosuppressants
    - MMF/MPA
    - AZA
    - CYC
- Biologics
    - Anti-CD20

    - Belimumab
    - Anifrolumab
- IVIG

Comparator: No therapy or HCQ alone

Outcomes:

- Reduction of myocarditis activity
- Overall disease activity
- Disease damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment -related adverse events: steroids: infection and osteoporosis; immunosuppressives including biologics and small molecules: infection and cytopenias; IVIG: headache

In SLE patients with Libman-Sacks endocarditis, what is the most effective therapy?

P65. In SLE patients with lupus Libman-Sacks endocarditis, does treatment with listed medical therapy vs HCQ treatment alone impact clinical outcomes?

Population: SLE patients with Libman-Sacks endocarditis defined as sterile vegetations on the valve surface or a thickened valve or valvulitis with or without vegetation (with or without aPL/APS, and with or without low complement levels).

Interventions:

- Anticoagulation
- Steroids
- Traditional Immunosuppressants and approved biologics (Belimumab, Anifrolumab)
- B-cell depletion (anti-CD-20 therapy)
- Surgical intervention (valvular surgery)

Comparators:

- Anticoagulation (AC) with vit K antagonists vs. no AC as comparator
- Steroid therapy vs. AC alone
- Steroid+ AC vs AC alone
- Immunosuppression + steroids vs AC
- Immunosuppression + steroids + AC vs AC
- B cell depletion therapy + steroids vs AC
- B cell depletion therapy + steroids + AC vs AC
- No surgical intervention vs (any) medical management

Outcomes:

- Size of the vegetations
- Valvular dysfunction requiring valve replacement / surgery
- Embolic disease (including stroke and TIA)
- Disease damage
- Mortality

- Quality of life
- Adverse impact of medications: bleeding for anticoagulation, infection and diabetes for steroid, infection and cytopenias for immunosuppressive medications.

F. Alternative treatments:
F1. Supplements – Address as GPS or text discussion
F2. Nonpharmacologic therapies – Address as GPS or text discussion
G. Other

- **Pregnancy / other reproductive health issues** – refer to reproductive health guideline
- **APS:** Text discussion, refer to recent relevant publications, emphasize importance in SLE, beyond scope of this GL