CLINICAL PRACTICE GUIDELINES

2023

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MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

Ministry of Health Malaysia

Malaysian Society of Rheumatology

Academy of Medicine Malaysia

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STATEMENT OF INTENT

This clinical practice guidelines (CPG) is meant to be a guide for clinical practice based on the best available evidence at the time of development. The guideline should not override the responsibility of the practitioners to make decision appropriate to the circumstances of the individual. This should be done in consultation with the patients and their families or guardians, taking into account the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2023 and will be reviewed in a minimum period of four years (2027) or sooner if there is a need to do so. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed. Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

TABLE OF CONTENTS

No.	Title	Page
	Levels of Evidence and Formulation of Recommendation	i
	Key Recommendations	ii
	Guidelines Development and Objectives	iv
	Development Group	vii
	Review Committee	viii
	External Reviewers	ix
	Algorithm 1: Diagnosis of SLE	x
	Algorithm 2: Treatment of Non-Renal SLE	xi
1.	**INTRODUCTION**	**1**
2.	**RISK FACTORS**	**2**
3.	**CLINICAL MANIFESTATIONS**	**3**
4.	**INVESTIGATIONS**	**5**
5.	**DIAGNOSIS AND CLASSIFICATION CRITERIA**	**9**
6.	**PRINCIPLES OF TREATMENT**	**11**
	6.1 Disease Assessment	11
7.	**TREATMENT**	**15**
	7.1 Non-Pharmacological Treatment	15
	7.2 Pharmacological Treatment	16
	a. Corticosteroids	16
	b. Antimalarial (Hydroxychloroquine)	17
	c. Immunosuppressants (Azathioprine, Methotrexate, Calcineurin Inhibitors, Cyclophosphamide, Leflunomide, Mycophenolate mofetil)	19
	d. Biologics (Belimumab, Rituximab, Anifrolumab)	22
	e. Nonsteroidal anti-inflammatory drugs	24
	f. Others (Plasma exchange/Plasmapheresis, Intravenous immunoglobulin)	24
8.	**SPECIFIC CLINICAL MANIFESTATION**	**27**
	8.1 Lupus Nephritis	27
	8.2 Mucocutaneous	28
	8.3 Neuropsychiatry	28
	8.4 Haematology	28
	8.5 Cardiorespiratory	29

TABLE OF CONTENTS

No.	Title	Page
9.	**MONITORING**	**30**
9.1	Clinical Features	30
9.2	Laboratory Investigations	30
9.3	Co-morbidities	31
9.4	Drug Adverse Events	33
9.5	Frequency and Interval	34
10.	**SPECIAL CONSIDERATION**	**35**
10.1	Antiphospholipid Syndrome	35
10.2	Pregnancy	36
10.3	Lactation	40
10.4	Adolescents	40
10.5	Vaccination	41
11.	**REFERRAL**	**43**
12.	**IMPLEMENTING THE GUIDELINES**	**44**
12.1	Facilitating and Limiting Factors	44
12.2	Potential Resource Implication	44
	REFERENCES	**46**
Appendix 1	Example of Search Strategy	54
Appendix 2	Clinical Questions	55
Appendix 3	2012 SLICC Classification Criteria for SLE	57
Appendix 4	2019 EULAR/ACR Classification Criteria for SLE	59
Appendix 5	Systemic Lupus Erythematosus Disease Activity Index - 2000 (SLEDAI-2K)	60
Appendix 6	British Isles Lupus Activity Group (BILAG) Index - 2004	62
Appendix 7	Medication in SLE	64
Appendix 8	Frequency of Monitoring Patients with SLE	70
Appendix 9	Sapporo Classification Criteria	72
Appendix 10	Recommendations on Types of Contraception for Patients with SLE	74
	List of Abbreviations	79
	Acknowledgement	79
	Disclosure Statement	79
	Source of Funding	79

LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

SOURCE: *U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG DG.
- Recommendations are formulated based on **certainty of evidence** and the wording used denotes the **strength of recommendations**. This takes into account:
  - quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - relevancy and applicability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word "should" being considered. Otherwise, weak recommendations use the word "may" in proposing an action to be made.
- In the CPG, a yellow box ☐ highlights important message(s) in the management while a blue box ☐ contains evidence-based recommendation(s) for the particular condition.

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group (DG) as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

DIAGNOSIS AND CLASSIFICATION CRITERIA

- Diagnosis of systemic lupus erythematosus should be based on clinical manifestations supported by laboratory findings following exclusion of alternative diagnoses.

PRINCIPLES OF TREATMENT

- All patients with systemic lupus erythematosus (SLE) should have clinical assessment of disease activity; this may be done using the validated assessment tools for SLE.

TREATMENT

- Patients with systemic lupus erythematosus (SLE) should practise sun avoidance, use protective clothing and broad-spectrum sunscreen with at least sun protection factor (SPF) 50.
- Corticosteroids should be used for acute flare in SLE; the dose should be minimised accordingly and discontinued whenever possible.
- All patients with SLE should be on hydroxychloroquine (HCQ) unless intolerant or contraindicated.
- Immunosuppressants should be considered as add-on therapy to patients with SLE not responding to HCQ alone or in combination with corticosteroids, or when corticosteroids doses cannot be tapered.
- Cyclophosphamide or mycophenolate mofetil may be used as induction therapy in certain major organ involvement in SLE.
- Biologics may be used as an adjunct therapy in active SLE despite standard therapy with corticosteroids and immunosuppressants.

MONITORING

- All patients with systemic lupus erythematosus (SLE) should be monitored based on clinical and laboratory parameters.
- Patients with SLE should be screened for cardiovascular risk factors and osteoporosis.
- Infection in patients with SLE should be identified early and treated accordingly.

SPECIAL CONSIDERATION

- All women with systemic lupus erythematosus (SLE) in the reproductive age group should receive pre-pregnancy counselling.
- In SLE with pregnancy, hydroxychloroquine, azathioprine, calcineurin inhibitors and low dose corticosteroids should be continued.
- Low dose aspirin should be initiated in all pregnant SLE patients unless intolerance or contraindicated.
- Vaccination status and indications for further vaccinations of patients with SLE should be assessed yearly.

GUIDELINES DEVELOPMENT AND OBJECTIVES
GUIDELINES DEVELOPMENT

The members of the DG for these CPG were from the Ministry of Health (MoH) and the Ministry of Higher Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases/platforms: mainly Medline via Ovid and others e.g. Pubmed (refer to **Appendix 1** for **Example of Search Strategy**). The inclusion criteria are all adults at risk and with systemic lupus erythematous (SLE) regardless of study design. The first search was limited to literature published in the last 13 years (2009 until 2022) for all clinical questions, on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted for studies related to the issues addressed. All searches were conducted from 21 February 2022 to 21 October 2022. The literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 1 July 2023 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat. The DG members take note that new documents on SLE by EULAR and Antiphospholipid Syndrome Classification Criteria by ACR/EULAR have been published recently after the cut-off date for retrieval of evidence of this MoH CPG.

References were also made to other guidelines on SLE as listed below:

- European Alliance of Associations for Rheumatology - 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus (2019 update)
- British Society for Rheumatology - The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults (2018)
- van Vollenhoven RF, Mosca M, Bertsias G, et al. - Treat-to-target in systemic lupus erythematosus: recommendations from an international task force (2014)

A total of 11 main clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2** for **Clinical Questions**. The DG members met 24 times throughout the development of these guidelines. All literature retrieved was appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meeting. All statements and recommendations formulated after that were agreed

upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion are resolved consensually. The CPG was based largely on the findings of systematic reviews/meta-analyses and clinical trials, with local practices taken into consideration.

The literatures used in these guidelines were graded using the U.S. Preventive Services Task Force Level of Evidence (2015) while the grading of recommendation was done using the principles of GRADE as much as possible (refer to the preceding page). The writing of the CPG followed strictly the requirement of Appraisal of Guidelines for Research and Evaluation (AGREE) II.

Upon completion, the draft CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the Health Technology Assessment (HTA) and CPG Council, MoH Malaysia, for review and approval. Details on the CPG development by MaHTAS can be obtained from **Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines** published in 2015 (available at https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf).).

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on the management of SLE on the following aspects:

- diagnosis and assessment
- treatment
- monitoring
- referral

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

Inclusion Criteria

- All adult patients suspected or diagnosed with SLE

Exclusion Criteria

- Drug-induced lupus
- Overlap syndrome
- Mixed connective tissue disease

TARGET GROUP/USERS

This document is intended to guide healthcare professionals and relevant stakeholders in primary and secondary/tertiary care of the management of SLE in adults including:

- healthcare professionals (doctors, pharmacists and allied health professionals)
- medical students and trainees
- policymakers
- professional organisations
- patients, caregivers and their advocates

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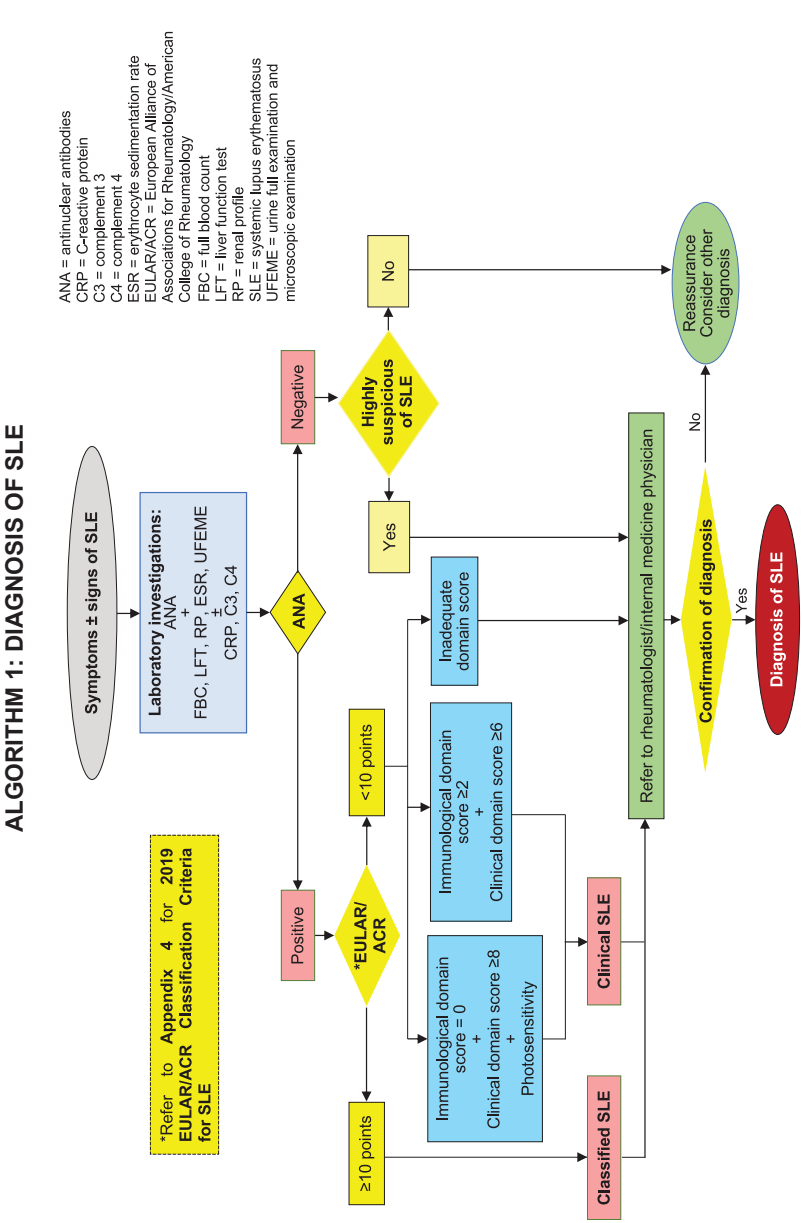
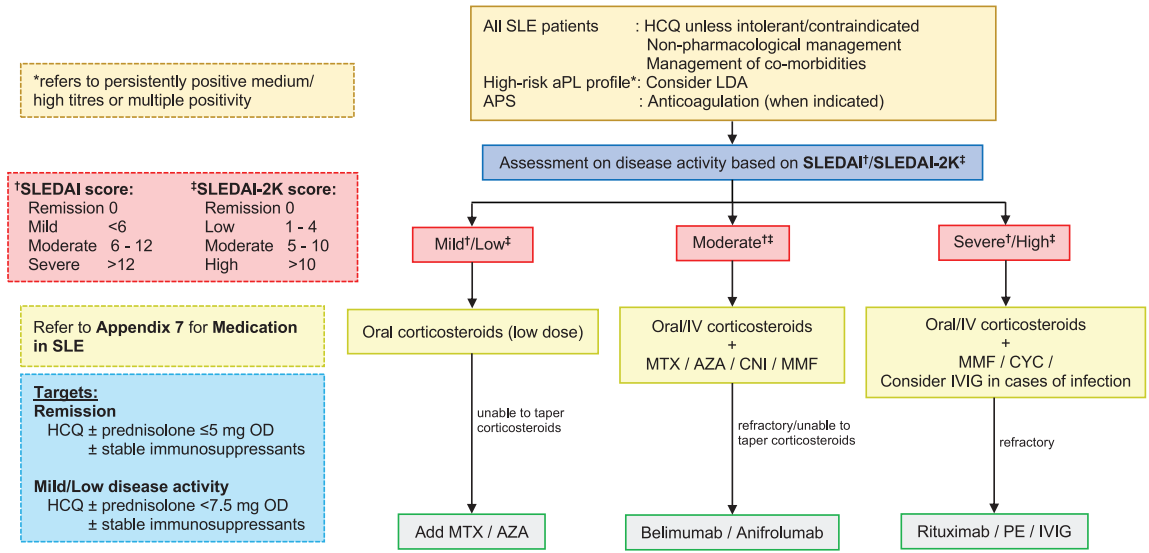

ALGORITHM 1: DIAGNOSIS OF SLE
ANA = antinuclear antibodies
CRP = C-reactive protein
C3 = complement 3
C4 = complement 4
ESR = erythrocyte sedimentation rate
EULAR/ACR = European Alliance of Associations for Rheumatology/American College of Rheumatology
FBC = full blood count
LFT = liver function test
RP = renal profile
SLE = systemic lupus erythematosus
UFEME = urine full examination and microscopic examination
Symptoms ± signs of SLE
Laboratory investigations:
ANA
+
FBC, LFT, RP, ESR, UFEME
±
CRP, C3, C4
ANA
Negative
Highly suspicious of SLE
No
Yes
Positive
*EULAR/ACR
<10 points
Inadequate domain score
Immunological domain score ≥2
+
Clinical domain score ≥6
≥10 points
Immunological domain score = 0
+
Clinical domain score ≥8
+
Photosensitivity
Clinical SLE
Classified SLE
Refer to rheumatologist/internal medicine physician
Confirmation of diagnosis
No
Reassurance
Consider other diagnosis
Yes
Diagnosis of SLE
*Refer to Appendix 4 for 2019 EULAR/ACR Classification Criteria for SLE

ALGORITHM 2: TREATMENT OF NON-RENAL SLE



aPL = antiphospholipid antibody
APS = antiphospholipid syndrome
AZA = azathioprine
CNI = calcineurin inhibitors
CYC = cyclophosphamide
HCQ = hydroxychloroquine

IV = intravenous
IVIG = intravenous immunoglobulin
LDA = low dose aspirin
MMF = mycophenolate mofetil
MTX = methotrexate
OD = once a day

PE = plasma exchange
SLE = systemic lupus erythematosus
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index - 2000

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune multisystem disorder with diverse and complex clinical manifestations characterised by inflammation in a variety of organs. The exact aetiology is unknown but genetic, hormonal and environmental factors have been implicated. This disease has a relapsing-remitting course with a very unpredictable prognosis and considerable morbidity.

The survival rates of patients with SLE have increased over the past few decades.[1, level II-2] These may be due to early disease detection, advancements in medical treatment and improved management of co-morbidities.

There was considerable variation in survival rates across the countries in Asia-Pacific region. The 5-year survival rates ranged from 60% among the Aborigines in Australia, 80% in Malaysia, 94% in South Korea and 98% in China (Shanghai), while 10-year survival rates ranged from 64% in Japan to 94% in Hong Kong.[2, level II-2] The leading causes of death among patients with SLE were infections and active disease predominantly in lupus nephritis (LN).[3, level II-2]

Patients with SLE commonly experience flares during the disease course which may have adverse impacts on the short- and long-term outcomes. The treat-to-target recommendations for SLE emphasises on targeting remission, preventing organ damage, minimising co-morbidities and drug toxicity, and improving health-related quality of life.[4]

Management of SLE in the Asian population remains a challenge due to limited access to health care, delayed diagnosis and poor treatment adherence.[5] The goal of this first national CPG on Management of SLE is to raise awareness among healthcare providers on early SLE detection, prompt referral to rheumatology services and initiation of treatment, mainly for non-renal SLE. The purpose of this CPG is to reduce the variation in practices and address resource implications in the management of SLE. This will encourage close cooperation between various stakeholders to enhance quality of life and outcomes of the affected patients through evidence-based management.

2. RISK FACTORS

Although the aetiology of SLE is multifactorial and not fully understood, identifying the risk factors associated with the development of SLE can help in predicting the probability of the disease in a patient.

a. Gender

SLE is more commonly diagnosed in women than men worldwide, with an incidence ranging from 1.4 to 5.4 cases per 100,000 population vs 0.4 to 0.8 cases per 100,000 population in men. The prevalence rate of SLE is also higher in women, ranging from 7.7 to 68.4 cases per 100,000 population vs 0.8 to 7.0 cases per 100,000 population in men.[2, level II-2]

In the Asia-Pacific region, a similar female preponderance of patients with SLE is consistently observed across different countries ranging from 83% to 97%.[2, level II-2; 6, level III]

b. Genetic factors

In a large cross-sectional study in Taiwan, a family history of SLE was found to be a strong risk factor for developing SLE:[7, level III]

- twins with RR of 315.94 (95% CI 210.66 to 473.82)
- siblings with RR of 23.68 (95% CI 20.13 to 27.84)
- parents with RR of 11.44 (95% CI 9.74 to 13.43)
- offspring with RR of 14.42 (95% CI 12.45 to 16.70)

Two case-control studies involving a Malay SLE cohort in Malaysia revealed that multiple alleles were associated with an increased risk of SLE, including HLA-A11 (OR=1.65, 95% CI 1.18 to 2.31), DQB105:01 (OR=1.84, 95% CI 1.37 to 2.48), HLA-DRB1*0405 (OR=3.493, 95% CI 2.103 to 5.801) and HLA-DRB1*1502 (OR=1.586, 95% CI 1.132 to 2.221).[8 - 9, level II-2]

c. Atopic disease

A meta-analysis showed that asthma was associated with SLE, with a pooled OR of 1.58 (95% CI 1.14 to 2.18).[10, level II-2] An earlier case-control study found SLE was associated with the following atopic diseases:[11, level II-2]

- asthma (OR=1.43, 95% CI 1.20 to 1.71)
- allergic rhinitis (OR=1.52, 95% CI 1.34 to 1.73)
- allergic conjunctivitis (OR=1.53, 95% CI 1.37 to 1.72)
- atopic dermatitis (OR=2.31, 95% CI 1.83 to 2.93)

d. Environmental

i. Smoking

In a large meta-analysis of moderate quality primary papers on the risk of developing SLE:[12, level II-2]

- current smokers had higher risk compared with never smokers (OR=1.49, 95% CI 1.06 to 2.08)
- ever smokers had higher risk compared with never smokers (OR=1.54, 95% CI 1.06 to 2.23)

ii. Silica exposure

A meta-analysis showed that the risk of SLE increased with occupational exposure to free crystalline silica (OR=9.72, 95% CI 1.13 to 83.58).[13, level II-2] An exposure-response effect was also seen for longer duration of exposure to silica (p for trend=0.01) in a case-control study:[14, level II-2]

- OR for exposure to silica for 1 - 5 years was 4.0 (95% CI 1.2 to 12.9)
- OR for exposure to silica for >5 years was 4.9 (95% CI 1.1 to 21.9)

e. Hormonal (contraceptive and hormone replacement therapy)

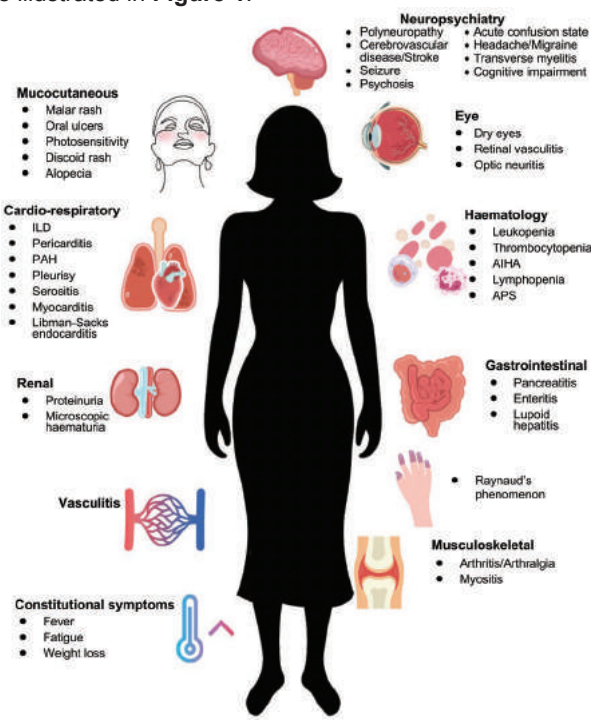
A meta-analysis showed an association between hormone replacement therapy (HRT) exposure and SLE development (RR=1.96, 95%, CI 1.51 to 2.56). However, there was no significant association between oral contraceptives and SLE.[15, level I] There was no mention of the quality assessment of the observational study used in the meta-analysis.

3. CLINICAL MANIFESTATIONS

The diagnosis of SLE is based on a combination of clinical and laboratory findings indicative of immune reactivity or inflammation in various organs. There are many mimickers for SLE that should be excluded before arriving at the diagnosis of the disease.

In a retrospective cohort study on SLE, the most frequent initial presenting symptoms were musculoskeletal, followed by mucocutaneous and neurological. The median time from first musculoskeletal symptom to SLE diagnosis was 26.4 months (IQR 9.3, 43.6). Sub-group analysis showed that the younger patients <30 years with severe disease had the shortest time to the diagnosis.[16, level II-2]

Common presentations include mucocutaneous, musculoskeletal, haematological and renal manifestations. The clinical manifestations of SLE are illustrated in **Figure 1**.



AIHA = autoimmune haemolytic anaemia; APS = antiphospholipid syndrome; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension

Figure 1: Clinical manifestations of SLE

Source:
1. Jasmin R, Sockalingam S, Cheah T, et al. Systemic lupus erythematosus in the multiethnic Malaysian population: disease expression and ethnic differences revisited. Lupus. 2013;22(9):967-971.
2. Shaharir SS, Hussein H, Rajalingham S, et al. Damage in the Multiethnic Malaysian Systemic Lupus Erythematosus (SLE) Cohort: Comparison with Other Cohorts Worldwide. PLoS One. 2016;11(11):e0166270.

4. INVESTIGATIONS

Detailed history taking, physical examination and laboratory evaluation are important to differentiate patients with SLE from those with lupus mimickers (e.g. infection, malignancy, medications or vaccine-related reactions). If SLE is suspected based on clinical findings, laboratory testing can be done to support the diagnosis.

Standard laboratory tests that are diagnostically useful when SLE is suspected include the following:

i. full blood count (FBC) with differential count
ii. renal parameters: renal profile (RP), urinalysis with microscopy for sediments, spot urine protein/creatinine ratio (UPCR) or 24-hour urine protein (24hUP)
iii. liver function tests
iv. acute phase reactants: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
v. autoantibodies: antinuclear antibodies (ANA), anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies, extractable nuclear antigens (ENA) and antiphospholipid antibodies (aPL)
vi. complement 3 (C3) and complement 4 (C4)

- **Full blood count**

A standard or differential blood count may reveal cytopenia e.g. thrombocytopenia and/or leukopenia and lymphopenia, as well as autoimmune haemolytic anaemia (AIHA). Anaemia is a common finding in patients with active lupus, either due to chronicity of the disease or iron deficiency.[17, level II-2]

- **Renal parameters**

Renal parameters should include RP and urine full examination and microscopic examination (UFEME) for sediments to screen for kidney involvement. The spot urine UPCR or 24hUP may be used to quantify proteinuria.

The 2012 American College of Rheumatology (ACR) guidelines state that findings for LN are:[18]

- persistent proteinuria >0.5 in UPCR or >0.5 g/day in 24hUP or urine dipstick ≥3+
- active urinary sediment (defined as >5 red blood cells [RBCs] per high power field [hpf]; >5 white blood cells [WBCs]/hpf in the absence of infection or cellular casts limited to RBC or WBC casts)

- **Liver function tests**

The standard liver function test (LFT) includes measurement of transaminases and serum albumin. Liver involvement in SLE is relatively rare and deranged LFTs can be due to a wide variety of aetiologies including lupus hepatitis or secondary to co-morbidities e.g. fatty liver or viral hepatitis.[19, level II-2] Hypoalbuminemia in SLE is associated with disease activity e.g. LN, protein-losing enteropathy and chronic lupus peritonitis with ascites.[20, level III]

- **Acute phase reactants**

ESR and CRP levels are the most widely used indicators of the acute phase response to inflammation. ESR is often raised in active SLE but is not a reliable marker of disease activity as it does not differentiate between active lupus and infection. CRP is usually normal or slightly elevated in the presence of serositis or arthritis. A significantly raised CRP often indicates infection, therefore patients need to be screened thoroughly for it.[21]

- **Antinuclear antibodies**

Autoantibodies to intracellular antigens, historically known as ANA, are serological biomarkers that have a central role in the diagnosis and classification of systemic autoimmune rheumatic diseases.

Testing for ANA should be performed only when there is a high clinical suspicion of SLE.[22] ANA is present in 95% of SLE patients. Negative test of ANA suggests a low clinical probability of the patients having SLE.[21]

ANA detection can be performed by enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IIF) and other techniques. The IIF using HEp-2 substrate is the “gold standard” for primary ANA detection because of its overall high sensitivity.[22] ELISA technique is less sensitive than IIF, but it has the advantages of being less laborious, less subjectivity in its interpretation and can be automated. For these reasons, ELISA technique is widely used locally; however IIF may be used for confirmation when indicated.

The 2019 European Alliance of Associations for Rheumatology/ American College of Rheumatology (EULAR/ACR) classification criteria for SLE include a positive ANA ≥1:80 by HEp-2 IIF at least once, as an obligatory entry criterion.[23]

- **Anti-double stranded deoxyribonucleic acid antibodies**

Anti-dsDNA antibodies react against antigenic determining factors present in the deoxyribonucleic acid (DNA). It is highly specific for the diagnosis of SLE with ≥90% specificity.[23; 24, level III] Anti-dsDNA antibodies are identified in 60 - 80% of SLE patients and only <2.5% in healthy controls.[23]

- **Extractable nuclear antigen autoantibodies**

Autoantibodies to ENA are important diagnostic markers for several systemic autoimmune diseases including SLE. Among ENA antibodies for SLE are anti-Smith (anti-Sm), anti-Sjögren's-syndrome-related antigen A (anti-SSA), anti-Sjögren's-syndrome-related antigen B (anti-SSB) and antibodies to ribonucleoprotein (anti-RNP).

Anti-Sm antibodies are highly specific and predictive but less sensitive compared with ANA in the diagnosis of SLE. They are never found in healthy individuals and rarely identified in patients with other rheumatic disease.[21; 23]

Anti-SSA and anti-SSB are also known as anti-Ro and anti-La autoantibodies respectively. Both have the highest prevalence in Sjögren's syndrome where the presence of anti-Ro antibodies constitutes a classification criterion. The prevalence of anti-Ro and anti-La antibodies in SLE patients is around 25 - 30% and 10 - 15% respectively.[25, level III]

Anti-RNP are antibodies against small ribonucleic acid (RNA) component of nuclear riboproteins and have structural similarities with anti-Sm antibodies. They are present in 25 - 40% of SLE patients.[25, level III]

Anti-SSA/SSB and anti-RNP antibodies are less-specific markers of SLE as they are found in other autoimmune rheumatic disorders as well as SLE.[21; 23] However, these antibodies were associated with pulmonary arterial hypertension in a case-control study on patients with SLE:[26, level II-2]

- anti-RNP (OR=12.399, 95% CI 3.581 to 42.934)
- anti-SSA (OR=4.836, 95% CI 1.675 to 13.598)

- **Antiphospholipid antibodies**

aPL are autoantibodies directed against phospholipid-binding proteins. The common clinical assays for aPL include lupus anticoagulant (LA)

test and ELISA tests for anticardiolipin antibodies (aCL) and anti-beta-2-glycoprotein 1 (anti-β2GP1). In SLE, 30 - 40% of patients are positive for aPL.[27, level II-2; 28, level III]

The presence of aPL is incorporated as an immunologic domain for classification of SLE. The aPL includes:[23; 29, level III]

- aCL antibodies (immunoglobulin A [IgA], immunoglobulin G [IgG] or immunoglobulin M [IgM]) at medium or high titre (>40 A phospholipids [APL], G phospholipids [GPL] or M phospholipids [MPL] units, or >99th percentile)
- anti-β2GP1 (IgA, IgG or IgM)
- LA

In antiphospholipid syndrome (APS), two tests with a minimum interval of 12 weeks are necessary in order to exclude short-term IgM antibodies following a vascular event or an infection.[30, level III]

- **Complements**

Complement activation is a key event in the pathogenesis of tissue inflammation and injury in SLE patients where decreased levels of C3 and C4 are detected along with disease activity. However, serum complement levels can be affected by various physiological conditions e.g. infections, traumatic damage or immunosuppressants, and not only in patients with autoimmune diseases but healthy individuals.[31, level III; 32, level III]

Apart from above, further investigations will depend on the symptoms of SLE that are present.[33, level III]

Recommendation 1

- The following tests should be done to assist in the diagnosis of systemic lupus erythematosus (SLE):
  - full blood count with differential counts
  - renal profile
  - liver function test
  - urinalysis
  - erythrocyte sedimentation rate with/without C-reactive protein
  - antinuclear antibodies and anti-double stranded deoxyribonucleic acid
  - complement 3 and complement 4
- All patients with SLE should be screened for antiphospholipid antibodies at diagnosis.

5. DIAGNOSIS AND CLASSIFICATION CRITERIA

There is no diagnostic criteria for SLE. Classification criteria has been used as a guide to identify several salient clinical features in establishing the diagnosis.

Four classification criteria that have been used are:

- 1982 revised American Rheumatism Association (ARA) SLE classification criteria[34, level III]
- 1997 ACR classification criteria revision[35, level III]
- 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria[36, level III]
- 2019 EULAR/ACR classification criteria[23]

ANA or other positive immunologic parameters (autoantibodies or hypocomplementemia) are required for classification of SLE according to the SLICC-2012 and EULAR/ACR-2019 but not the ACR-1997 criteria.[23]

The EULAR/ACR-2019 criteria for SLE include positive ANA (a titer of ≥1:80 on Hep-2 cells) at least once as an obligatory entry criterion. It is followed by additive weighted criteria grouped in seven clinical and three immunological domains. Each criterion in both domains is weighted from 2 to 10. Patients accumulating ≥10 points are classified as SLE. In the validation cohort, the sensitivity of EULAR/ACR-2019 is comparable with SLICC-2012 but higher than ACR-1997. Meanwhile, the specificity of EULAR/ACR-2019 is similar with ACR-1997 but higher than SLICC-2012 (refer to Table 1).[23]

Table 1: Sensitivity and specificity of three classification criteria for SLE

Parameter	EULAR/ACR-2019	SLICC-2012	ACR-1997
Sensitivity	96.1% (95% CI 95 to 98)	96.7% (95% CI 95 to 98)	82.8% (95% CI 80 to 85)
Specificity	93.4% (95% CI 91 to 95)	83.7% (95% CI 80 to 87)	93.4% (95% CI 91 to 95)

In a local cross-sectional study on Malaysian SLE patients, EULAR/ACR-2019 and SLICC-2012 criteria had higher sensitivities than ACR-1997. The EULAR/ACR-2019 showed comparable specificity to the ACR-1997 and SLICC-2012 as shown below (refer to Table 2).[37, level III]

Table 2: Sensitivity and specificity of three classification criteria for SLE in a Malaysian study

Parameter	EULAR/ACR-2019	SLICC-2012	ACR-1997
Sensitivity	90.8% (95% CI 85 to 94)	96.1% (95% CI 92 to 98)	82.0% (95% CI 75 to 86)
Specificity	94.0% (95% CI 87 to 97.5)	94.0% (95% CI 86 to 97)	96.0% (95% CI 89 to 98)

Refer to **Appendix 3** for **2012 SLICC Classification Criteria** for **SLE** and **Appendix 4** for **2019 EULAR/ACR Classification Criteria for SLE.**

- Classification criteria are not diagnostic criteria. It is used to identify a relatively homogeneous groups of patients for inclusion in research.

Recommendation 2

- Diagnosis of systemic lupus erythematosus (SLE) should be based on clinical manifestations supported by laboratory findings following exclusion of alternative diagnoses.
- Classification criteria should not be used for the diagnosis of SLE.

6. PRINCIPLES OF TREATMENT

Due to its multisystem involvement, SLE may present with a myriad of possible clinical manifestations, making it a challenge to diagnose and treat.

- Principles of SLE treatment are to achieve:
  - disease remission
  - disease flare prevention
  - organ damage prevention
  - quality of life improvement
  - minimisation of drug side effects
- If complete remission cannot be achieved, the lowest possible disease activity in all organs involved should be targeted.

6.1 Disease Assessment

Patients with SLE may have a fluctuating disease course or persistently active disease despite being on medications. Both persistent disease activity and disease flares can contribute to irreversible damage and impact health-related quality of life. The principal goal of SLE treatment according to the 'treat-to-target' approach emphasises minimisation of disease activity.[4] Achieving remission in SLE is desirable but not always attainable, hence low disease activity state is an acceptable alternative.

SLE flare is generally defined as any increase in disease activity leading to intensification of therapy. It refers to a measurable increase in disease activity in one or more organ systems involving new or worsening clinical signs and symptoms and/or laboratory measurements. It must also be considered clinically significant to warrant adjustment of treatment.[38, level III]

Disease activity in SLE can be measured as clinical activity (inflammation of organs) or serological activity (elevated anti-dsDNA antibodies or low complements levels). In clinical practice, disease activity in SLE can be evaluated by assessment of symptoms, signs and laboratory tests including serology. There are many disease activity assessment tools in SLE, however these were created mainly for clinical trials. The commonly used and validated tools are (**Table 3**):

- Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) in its original version or improved versions which are Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI or SLEDAI 2000 (SLEDAI-2K)
- British Isles Lupus Activity Group index (BILAG)-2004

All three SLEDAIs have the same items (24 clinical presentations within a period of 10 days) and weightage (1 to 8 [range 0 - 105]) with some

variations for the definition of certain items. The items are scored if present and attributed to active lupus. Increment of SLEDAI-2K or SELENA-SLEDAI score ≥3 indicates mild or moderate lupus flare. A severe flare is indicated by SELENA-SLEDAI score >12.[39, level I; 40, level III]

BILAG-2004 differs from SLEDAI because it evaluates activity for each organ whereas SLEDAI only describes disease activity by the total score. The classic BILAG index was revised several times and BILAG-2004 (which was also revised in 2009) is currently used. There are 97 items in nine domains and each item is scored 0 (not present) to 4 (new) by evaluating activity in the last four weeks compared with the previous four weeks. Each organ domain also has severity assessment from A (severe) to E (no evidence).

Refer to **Appendix 5** for **SLEDAI-2K** and **Appendix 6** for **BILAG-2004**.

Table 3: Disease Activity Assessment Tools for SLE

	Disease activity		
Assessment tool	**Mild**	**Moderate**	**Severe**
BILAG[1]	BILAG C scores or single B score	BILAG 2 or more systems with B scores	(Non-renal) BILAG 1 or more A scores
SLEDAI	<6	6 - 12	>12
	Disease activity		
Assessment tool	**Low**	**Moderate**	**High**
SLEDAI-2K[2]	1 - 4	5 - 10	>10

*SLEDAI/SLEDAI-2K score of 0 is categorised as remission

Source:

1. Gordon C, Amissah-Arthur MB, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology. 2018;57(1):e1-45.
2. Gladman DD, Ibañez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol. 2002;29(2):288-291.

The 2021 Definition of Remission in SLE (DORIS) is defined as clinical SLEDAI score of 0 and Physician Global Assessment (PGA) <0.5 irrespective of serological status. The patient may be on antimalarials, low dose corticosteroids (prednisolone <5 mg/day), and/or stable immunosuppressants including biologics.[41, level III]

Lupus low disease activity state (LLDAS) is an alternative goal for patients. The definition must include the following components:[42, level III]

- SLEDAI-2K ≤4 points (with no activity in major organ systems and no new features of activity compared with previous assessment)
- PGA ≤1.0 point

- minimal prednisolone dose of ≤7.5 mg/day
- on standard maintenance doses of immunosuppressive drugs and/or approved biological agents

It is estimated that 20 - 25% of SLE patients will flare within 1 - 2 years and 40 - 66% within 5 - 10 years after achievement of a low disease activity or remission. The risk factors for SLE flare include:[43, level III]

- male gender
- age of SLE onset ≤25 years
- major organ involvement (cytopenias, neuropsychiatric, nephritis, vasculitis)
- persistent clinical disease activity
- low serum C3/C4
- high anti-dsDNA antibodies
- poor compliance to treatment
- discontinuation or have never been on HCQ
- rapid tapering or withdrawal of maintenance immunosuppressive treatment

Smoking and ultraviolet radiation have been shown to trigger or aggravate cutaneous lupus erythematosus (CLE) manifestations.[44 - 45, level III] There is a small increase in risk of mild to moderate lupus flares with use of oral HRT.[46]

In a meta-analysis of moderate quality primary studies on the effect of disease activity and damage of patients with SLE, it was found that there were:[47, level I]

- greater risk of mortality in patients with higher SLEDAI disease activity (HR=1.14, 95% CI 1.06 to 1.22)
- greater risk of damage in patients with higher SLEDAI scores as measured by SLICC/ACR Damage Index (SDI) (HR=1.18, 95% CI 1.02 to 1.37)
- higher risk of mortality in patients with worse damage as measured by SDI (HR=1.44, 95% CI 1.29 to 1.61)

The above findings were supported by a large meta-analysis that showed organ damage with greater SDI in SLE was consistently associated with increased mortality (HR=1.34, 95% CI 1.24 to 1.44). Most of the primary studies were of high-quality.[48, level II-2]

There is no standard definition of refractory disease in SLE. The CPG DG opines that it may be defined as persistent disease activity despite optimal standard therapy. However, it is important to ensure the diagnosis is accurate and, persistent symptoms and signs are derived primarily from SLE activity and not from concomitant diseases (e.g. infections, atherosclerosis or other autoimmune diseases) or adverse events (AEs) of drugs.[49, level III]

Recommendation 3

- All patients with systemic lupus erythematosus (SLE) should have clinical assessment of disease activity.
  - This may be done using the validated assessment tools for SLE.

7. TREATMENT

7.1 Non-Pharmacological Treatment

There is limited evidence on the non-pharmacological treatment of SLE.

a. Sun protection

Sunlight can induce or exacerbate SLE in a wide variety of cutaneous manifestations including discoid lupus erythematosus and acute CLE. These conditions may lead to physical and psychological burden to patients.

Two guidelines recommend the use of broad-spectrum sunscreen for effective protection against ultraviolet exposure.[21; 50] This is supported by a systematic review that showed application of sunscreen with sun protection factor (SPF) 50 - 75 reduced lesion development in the setting of photo-provocation among patients with CLE.[51, level I]

In addition, patient should be advised on sun avoidance and the use of protective clothing.[21]

b. Nurse-led care

Patients with SLE face a unique set of challenges due to the variability of the symptoms experienced. Nurses play an important role in addressing these challenges by providing a multitude of nurse-led interventions such as patient educational sessions, counselling, exercise and transitional care programs. A randomised controlled trial (RCT) among patients with SLE showed that transitional care programmes led by specialist nurses compared with usual care group had significant improvement in patient self-care and quality of life as well as reduction in readmission rate up to 90 days.[52, level I]

c. Physiotherapy/exercise and psychological therapy

In a systematic review on patients with SLE, combination of physical activity (aerobic exercise) or psychological interventions (psychoeducation, mindfulness-based cognitive therapy and biofeedback-assisted cognitive behaviour therapy with relaxation techniques) with usual medical care was compared with usual medical care alone. The combined treatment was more effective in improving fatigue, psychological function, pain and quality of life.[53, level I] However, quality assessment of primary studies was not reported.

A recent Cochrane systematic review assessed the effectiveness of exercise as an adjunct to pharmacological treatment. The intervention was only more effective compared with other non-pharmacological treatments adjunct to pharmacological treatment in fatigue, functional capacity and pain. The quality of primary papers used was generally low to very low.[54, level I]

A wellness program providing social support, lifestyle and stress management training among patients with SLE led by a lupus foundation showed improved self-care knowledge, health behaviours, mental health status and quality of life.[55, level II-3]

Recommendation 4
- Patients with systemic lupus erythematosus should practise sun avoidance and, use protective clothing and broad-spectrum sunscreen with at least sun protection factor (SPF) 50.

7.2 Pharmacological Treatment

Pharmacological treatment in SLE aims to suppress the disease activity. Drug treatment is individualised according to the clinical presentation of the disease and the varying disease activity. Corticosteroids are the cornerstone treatment in SLE, with immunosuppressants being the gold standard treatment for major organ involvement. The initial period of intensive immunosuppressive treatment, also known as induction therapy, aims at halting immunological activity especially when there is high disease activity or major organ involvement. This is followed by a less aggressive maintenance treatment to consolidate remission and reduce risk of disease flare. Drugs used in the treatment of SLE may have AEs which require close monitoring for toxicity. Minimum long-term treatment is necessary to maintain remission or low disease activity. Treatment should be based on a shared decision-making process between the patient and the clinician.

Refer to **Appendix 7** for **Medication in SLE**.

a. Corticosteroids

Corticosteroids have anti-inflammatory properties with rapid onset of action that is useful in mild to severe SLE. Although there is no new retrievable evidence on its effectiveness, it remains the cornerstone of SLE treatment despite advances in immunosuppressive drugs and therapeutic protocols, and development of new drugs.[56, level III]

Long-term use of corticosteroids may lead to various AEs. In a large cohort of SLE patients in Taiwan, the common AEs and their incidence rate are shown below.[57, level II-2]

Adverse event	Incidence rate (per 1000 person-years)
Peptic ulcer	147.84
Bacterial infection	136.42
Fungal infection	42.26
Hypertension	37.67
Osteoporosis	28.17
Fracture	23.77
Tuberculosis	7.85

A meta-analysis of eight small RCTs looked into rate of AEs related to medium to high dose of corticosteroids in patients with SLE. The pooled rates were 25/100 patients/year for infections, 12/100 patients/year for avascular necrosis of the hip and 9/100 patients/year for hyperglycaemia/diabetes.[58, level I] However, quality assessment for primary studies was not mentioned.

The risk of any new organ damage significantly increases with higher corticosteroids dosage.[59, level II-2]

- The doses and routes of corticosteroids administration should be based on the severity of organ involvement. The dose should be minimised during long-term treatment and discontinued when possible.[21; 50]

Recommendation 5
- Corticosteroids should be used for acute flare in systemic lupus erythematosus.
  - The dose should be minimised accordingly and discontinued whenever possible.

b. Antimalarial (Hydroxychloroquine)

Hydroxychloroquine (HCQ) is an anti-malarial drug with anti-inflammatory and immunomodulator effects. Long-term use of HCQ has been shown to ameliorate active SLE manifestations, improve immunologic parameters and disease activity scores, prevent disease flares and sustain remission. HCQ is the mainstay of lupus treatment and is recommended to be used in SLE unless intolerant or contraindicated.[18; 21; 50]

In a large systematic review of RCTs and observational studies, HCQ use was shown to reduce the rate of flares, achieve higher remission rate of membranous LN and protect against irreversible organ damage,

thrombosis and bone mass loss compared with control in SLE.[60, level I] However, the quality assessment of primary studies was not reported.

A prospective cohort study showed that the use of HCQ reduced the risk of death (HR=0.46, 95% CI 0.29 to 0.72) and renal damage (HR=0.30, 95% CI 0.13 to 0.68) compared with non-HCQ use in patients with SLE.[61, level II-2]

In a retrospective cohort study among patients in the maintenance phase of SLE, there were no significant difference between usual dose HCQ (5 mg/kg) and low dose HCQ (200 mg) in SLEDAI, Cutaneous Lupus Erythematous Disease Area and Severity Index (CLASI) and serum levels of anti-dsDNA antibodies at 6-month.[62, level II-2]

A systematic review of mixed study designs in SLE showed higher odds of flare in patients with low HCQ levels (<1000 ng/mL) compared with high levels (OR=5.89, 95% CI 1.38 to 25.08). The overall risk of bias assessment of primary studies in the review showed the eight observational studies were of fair to good quality while the three interventional studies were of unclear to low risk.[63, level II-2] HCQ adherence can be assessed using drug levels in the blood but it has not been recommended in routine clinical practice at present.

Long-term use of HCQ treatment is safe. Toxicity related to HCQ is infrequent, mild and usually reversible.[60, level I]

Specifically, retinal toxicity related to HCQ is uncommon. A retrospective cohort study on newly diagnosed SLE patients showed an incidence of HCQ retinal toxicity at one in 1000 person-years.[64, level II-2] However, the incidence increased in SLE patients with risk factors (e.g. long duration and high dose of HCQ) for toxic retinopathy.[65] In a case-control study on SLE, a small proportion (5.5%) of patients developed antimalarial-induced retinal complications over an average usage of 12.8 years. No retinal toxicity was reported in the first five years of exposure.[66, level II-2] The American Academy of Ophthalmology recommends HCQ dose of no more than 5 mg/kg actual body weight to reduce the occurrence of retinopathy.[65]

Recommendation 6

- All patients with systemic lupus erythematosus (SLE) should be on hydroxychloroquine (HCQ) unless intolerant or contraindicated.
- Ophthalmologic assessment should be done for patients with SLE on HCQ at baseline, and then:
  - yearly in the presence of known retinopathy risk factors*
  - after five years and yearly thereafter in the absence of retinopathy risk factors*

*The major risk factors for toxic retinopathy include long-term use and/or use of high dose HCQ, concomitant hepatic and renal disease, concomitant tamoxifen, history of retinal and macular disease and advanced age.[65; 67]

HCQ use during pregnancy and breast-feeding is considered safe.[46] Refer to **Subchapter 9.2** for HCQ Effectiveness and Safety in Pregnant Patients with SLE.

c. Immunosuppressants

Immunosuppressants are used in the treatment of lupus when there is involvement of major organ or life-threatening manifestations. They are also used to control active disease with inadequate response to corticosteroids alone, to prevent lupus flare and as steroid-sparing agents. The selection of immunosuppressants is guided by the organ involvement, disease severity, pregnancy and lactation compatibility, co-morbidities, safety concerns and cost.

i) Azathioprine

Azathioprine (AZA) causes immunosuppression by inhibiting the synthesis of purines that are needed in the DNA and RNA sequencing for the production of WBCs. It is used as a steroid-sparing agent in non-renal SLE and maintenance treatment in renal SLE (refer to **Subchapter 7.1**).

An RCT in a systematic review on patients with non-renal SLE showed both AZA and ciclosporin significantly reduced the mean dose of corticosteroids by >50% at 12 months compared with baseline. There was no significant difference between the two drugs at end point. The reported AEs included leukopenia, respiratory tract infection and rash.[68, level I]

European Alliance of Associations for Rheumatology (EULAR) 2019 and British Society for Rheumatology (BSR) 2018 guidelines recommend that AZA should be considered as add on therapy in non-renal lupus e.g. arthritis and cutaneous disease if HCQ is unable to control disease activity or when corticosteroids doses cannot be tapered.[21; 50]

ii) Methotrexate

Methotrexate (MTX) is an antimetabolite which is commonly used in the treatment of autoimmune diseases. It can be administered in oral or subcutaneous form. MTX is often used to treat musculoskeletal and cutaneous manifestations inadequately controlled with HCQ and corticosteroids. Folate supplementation is used to ameliorate MTX-associated AEs and toxicity (minimum dose of 5 mg/week).

In a systematic review of SLE treatment, two good quality RCTs showed that MTX was more effective than placebo based on:[68, level I]

- reduction in SLEDAI and Visual Analogue Scales (VAS) score at six months ($p<0.05$)
- reduction in Systemic Lupus Activity Measure-Revised (SLAM-R) at 12 months (MD= -0.86, 95% CI -1.7 to -0.02)
- reduction in SLAM-R in patients with SDI=0 at 12 months (MD= -1.41, 96% CI -2.42 to -0.39)
- reduction in corticosteroids dose in 65% of patients at six months ($p<0.001$)
- reduction in mean corticosteroids daily dose at 12 months (MD= -22.3, 96% CI -36.2 to -5.4)
- reduction in lupus flare at three and six months of treatment duration ($p=0.02$)
- improvement in arthralgia/arthritis and discoid SLE/malar rash at six months ($p<0.001$)

A non-randomised, open-labelled, control study among patients with SLE on prednisolone taper showed MTX compared with non-MTX group was more effective in improving serological abnormalities in terms of:[69, level II-1]

- increment of complement levels at three, six and 12 months ($p<0.01$) and normalisation or elevation in C3 and/or C4 levels at 18 months ($p=0.0001$)
- reduction in dsDNA levels at three, six and 12 months ($p<0.01$) and normalisation or reduction of anti-dsDNA antibodies at 18 months ($p=0.0022$)

It was also more effective in reducing the following outcomes:

- SLEDAI score at six, 12 and 18 months ($p<0.01$)
- prednisolone dose at 12 and 18 months ($p<0.05$)

MTX was reported to have good safety profile with gastrointestinal (GI) symptoms and hepatotoxicity being the most frequent AEs.[68, level I; 69, level II-1]

iii) Calcineurin inhibitors

Ciclosporin and tacrolimus are calcineurin inhibitors (CNI) that inhibit calcineurin phosphatase, which is involved in the production of interleukin-2, a molecule that promotes the development and proliferation of T-lymphocytes as part of the body's adaptive immune response.

- **Ciclosporin**

In a systematic review on immunosuppressants, an RCT showed that ciclosporin in combination with corticosteroids reduced SLEDAI scores ($p<0.05$) and cumulative corticosteroids dose ($p<0.005$) compared with

corticosteroids alone in patients with moderate non-renal SLE at 12 months. The second RCT demonstrated that ciclosporin also reduced the mean dose of corticosteroids by >50% compared with baseline ($p<0.001$) in patients with severe non-renal SLE at 12 months. The first RCT had a score of 1 while the second had a score of 3 based on Jadad scale.[68, level I]

The reported AEs in the review included hypertension, respiratory tract infection and anaemia.[68, level I] Additionally, other common AEs include hypertrichosis, gum hypertrophy, paraesthesia, tremor, GI symptoms and impaired renal function, especially at higher doses (>3 mg/kg/day).[21]

- **Tacrolimus**

In a systematic review, a cohort study demonstrated that tacrolimus 1 - 3 mg/day significantly reduced mean SLEDAI scores and dose of prednisolone in SLE patients without active nephritis after one year. Non-serious AEs were observed in 40% of the cohort. However, quality assessment of the study was not reported.[68, level I]

iv) Cyclophosphamide

Cyclophosphamide (CYC) is a non-specific alkylating agent that prevents cell division by forming cross-linkages in DNA, which leads to inhibition of T and B lymphocytes proliferation.

A small, low quality RCT in a Cochrane systematic review studied neuropsychiatric SLE (NPSLE). The patients had IV induction of methylprednisolone and tapering oral prednisolone. Comparison between CYC and continuation of methylprednisolone showed the former was more effective in achieving 20% improvement in clinical, serological and specific neurological measures, improvement of SLEDAI score and reduction of prednisolone requirements. There was no significant differences in AEs and deaths.[70, level I]

Another systematic review that included two small RCTs on NPSLE showed that CYC in combination with corticosteroids was more effective than corticosteroids alone in the following outcomes:[68, level I]

- clinical improvement at six months ($p=0.005$)
- reduction of relapses at three months ($p=0.005$)
- electroencephalogram improvement ($p=0.003$)
- ≥20% improvement in clinical, serological and neurological measures at two years ($p<0.03$)

There was no difference in AE in one of the RCTs. Both RCTs scored 1 - 3 on Jadad scale.

The use of CYC in renal SLE is mentioned in **Subchapter 7.1**.

v) Leflunomide

Leflunomide is a pyrimidine synthesis inhibitor with anti-inflammatory properties.

In a systematic review on mild to moderate active SLE, leflunomide was more effective than placebo in reducing SLEDAI at 24 weeks (11.0±6.1 vs 4.5±2.4; p=0.02) but there were no significant differences in proteinuria, complement, anti-dsDNA antibodies and corticosteroids dose. There were also no difference in AEs between the two groups.[68, level I]

Leflunomide may be considered in moderate lupus refractory/intolerant/ not suitable for other immunosuppressants. It may also be considered when CYC and biological agents are not suitable or not available.[21]

vi) Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an immunosuppressant used for SLE patients with both renal and non-renal involvement.

The use of MMF in renal involvement of SLE is well established. A systematic review included a report on the secondary non-renal outcomes of the Aspreva Lupus Management Study (ALMS), a large RCT on induction treatment for LN. The RCT showed MMF (0.5 g/12 h and increased to 1.5 g/12 h) had comparable effectiveness with CYC 0.5 - 1 g/m2/month in improving BILAG scores, inducing remission in the mucocutaneous, musculoskeletal and cardiovascular (CV)/ respiratory systems as well as reducing SELENA-SLEDAI flares at six months.[68, level I]

Recommendation 7

- Immunosuppressants should be considered as add-on therapy to patients with systemic lupus erythematosus (SLE) not responding to hydroxychloroquine (HCQ) alone or in combination with corticosteroids, or when corticosteroids doses cannot be tapered.
- Immunosuppressants may be considered in active SLE patients with HCQ intolerance.
- Cyclophosphamide or mycophenolate mofetil may be used as induction therapy in certain major organ involvement in SLE.

d. Biologics

Biologics are used as adjunct therapy in active SLE despite optimal treatment with corticosteroids and immunosuppressants. They may also be considered in refractory diseases and/or when there is intolerance or contraindication to standard treatment.

i) Belimumab

Belimumab is a recombinant, fully human monoclonal antibody that inhibits the biologic activity of B-lymphocyte stimulator (BLyS), also known as B-cell activating factor (BAFF). This agent is indicated as an adjunct therapy in patients with active SLE who are receiving standard therapy and for the treatment of LN.[71, level III]

In a Cochrane systematic review of six RCTs on SLE, belimumab was more effective than placebo in terms of:[72, level I]

- reduction of at least 4-point in SELENA-SLEDAI score (RR=1.33, 95% CI 1.22 to 1.45)
- improvement in quality of life based on 36-item short-form (SF-36) (MD=1.60, 95% CI 0.30 to 2.90)
- reduction in corticosteroids dose by at least 50% (RR=1.59, 95% CI 1.17 to 2.15)

In another systematic review of 12 studies which included seven RCTs, belimumab was more effective than placebo in SLE patients based on SLE Responder Index (SRI).[73, level I]

Belimumab was reported to have a good safety profile.[72 - 73, level I]

ii) Anifrolumab

Anifrolumab is a human monoclonal antibody to type I interferon receptor subunit 1. It is a newly approved adjunct therapy for patients with moderate to severe SLE.

In a landmark RCT among patients with moderate to severe SLE (Treatment of Uncontrolled Lupus via the Interferon Pathway [TULIP]-2), anifrolumab was more effective than placebo in terms of:[74, level I]

- higher percentage of British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) responder at week 52 (difference=16.3%, 95% CI 6.3 to 26.3)
- reduction of corticosteroids dose (difference=21.2%, 95% CI 6.8 to 35.7)
- reduction of CLASI by ≥50% at week 12 (difference=24.0%, 95% CI 4.3 to 43.6)

The most frequent AEs among patients on anifrolumab reported in this trial were upper respiratory tract infection, nasopharyngitis, infusion-related reaction, bronchitis and herpes zoster.

iii) Rituximab

Rituximab is a chimeric anti-CD20 antibody that induces peripheral B-cells depletion.

In a landmark study on non-renal SLE (The Exploratory Phase II/III SLE Evaluation of Rituximab [EXPLORER] trial), rituximab showed no significant difference with placebo in major or partial clinical response via the BILAG at week 52.[75, level I] However a systematic review of mainly moderate quality observational studies showed that rituximab had a steroid-sparing effect, in addition to improvement in disease activity and immunologic parameters.[76, level I]

Two guidelines support the use of rituximab in organ threatening, refractory moderate and severe lupus, intolerance/contraindications to standard immunosuppressive agents and as steroid sparing therapy.[21; 50]

Rituximab also had good safety profile where most frequent AEs were infusion reactions and infections.[76, level I]

Recommendation 8
- Biologics may be used as an adjunct therapy in active systemic lupus erythematosus (SLE) despite standard therapy with corticosteroids and immunosuppressants.
- Biologics may be considered in refractory disease of SLE, intolerance or contraindication to standard treatment.

e. Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to relieve pain and reduce inflammation due to their analgesic and anti-inflammatory effects. There is no retrievable latest evidence on its effectiveness as its use has been established and well-tolerated for short-term symptomatic relief. NSAIDs may be used cautiously in non-renal mild SLE (e.g. inflammatory arthralgia or myalgia) when there is intolerance or poor response to paracetamol. There is also potential increased risk of renal, hepatic and CV toxicity when NSAIDs are used in SLE patients.[21; 61, level II-2]

f. Others

i) Plasma exchange/Plasmapheresis

Plasma exchange (PE) or plasmapheresis is a therapeutic intervention that involves extracorporeal removal of high molecular weight substances (e.g. circulating immune complexes, autoantibodies and other immune reactants) involved in the pathogenesis of SLE with subsequent return or exchange of blood plasma or components. It has been utilised as an alternative therapeutic modality in selected patients with acute life-threatening manifestations, rare complications and severe treatment-refractory disease, in particular LN.

In a retrospective cohort study of renal biopsy-proven thrombotic microangiopathy LN, plasmapheresis treatment had higher rate of complete/partial remission compared with control (non-plasmapheresis) (77.8 vs 11.1%, p=0.018). No AEs were observed.[77, level II-2]

In a pre-post study of refractory SLE patients with sub-phenotypes of thrombotic thrombocytopenic purpura (TTP), myasthenia gravis and APS, PE as add-on treatment to corticosteroids and immunosuppressive agents significantly decreased SLEDAI. However, 21% patients experienced PE-related major AEs (catheter infections, bleeding and hypotension).[78, level II-3]

The BSR 2018 guidelines recommends the use of PE in SLE with TTP.[21] Meanwhile in the 2020 Chinese Guidelines for the Diagnosis and Treatment of Systemic Lupus Erythematosus, PE can be considered in patients with severe or refractory SLE.[67]

- PE is considered in patients with severe or refractory SLE, in particular those with TTP.

ii) Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is a blood product derived from the plasma of a large pool of healthy donors. The indication of its use as immunomodulator has expanded to treat various autoimmune and inflammatory diseases. There is limited evidence on IVIG treatment in SLE.

In a non-randomised controlled trial in LN patients, IVIG was not significantly different to CYC or AZA in achieving partial or complete renal remission following induction therapy. However, it had lower infection rate. No leukopenia, amenorrhoea or osteoporosis were observed.[79, level II-1]

- In SLE, the use of IVIG maybe considered in:[21; 50; 67]
  - severe refractory SLE including haematological flare, TTP and the catastrophic variant of APS
  - active SLE with concomitant infection

Thromboembolic events are delayed AEs of immunoglobulin treatment with incidence rate up to 2% when given in high dose.[80, level III] It occurs because of hyperviscosity especially in patients having risk factors including advanced age, previous thromboembolic diseases, bedridden, diabetes mellitus, hypertension, dyslipidaemia and those

receiving IVIG in high dose or by rapid infusion.[81, level III] It has therefore been suggested that a slow infusion rate of low concentration of IVIG products may reduce the thromboembolic events.[80, level III]

8. SPECIFIC CLINICAL MANIFESTATIONS

SLE is a multisystemic disease requiring comprehensive treatment which is determined by the disease severity and organ/system involved.

8.1 Lupus Nephritis

LN is classified according to the International Society of Nephrology and the Renal Pathology Society in 2003 as shown below:[82, level III]

Class	Incidence rate (per 1000 person-years)
I	Minimal mesangial LN
II	Mesangial proliferative LN
III	Focal LN (active and chronic; proliferative and sclerosing)
IV	Diffuse LN (active and chronic; proliferative and sclerosing; segmental and global)
V	Membranous LN
VI	Advanced sclerosis LN

For class I LN, treatment should be guided by symptoms whereas for class II, low dose prednisolone should be initiated and followed by an immunosuppressant if there is persistent proteinuria for more than three months or prednisolone dependency.

Treatment of class III and class IV LN includes an initial induction phase, followed by a more prolonged maintenance phase. MMF and CYC are the agents of choice for induction treatment. MMF or AZA may be used as maintenance treatment, with the former associated with fewer relapses. CNIs may be considered as second-line agents for induction or maintenance treatment mainly in membranous LN (class V) or in proliferative disease with refractory nephrotic syndrome despite standard treatment within 3 - 6 months.[50] For class VI LN, treatment is as per advanced chronic kidney disease (refer to **CPG Management of Chronic Kidney Disease [Second Edition]**).[83]

A landmark RCT (Lupus Nephritis Assessment with Rituximab [LUNAR] trial) on class III and class IV LN patients treated with MMF and corticosteroids showed that rituximab led to more responders and greater reductions in anti-dsDNA antibodies and C3/C4 levels. However, it did not improve clinical outcomes after one year of treatment.[84, level I]

According to the Belimumab in Subjects with Systemic Lupus Erythematosus (BLISS)-LN trial, IV belimumab was superior to placebo as an add-on therapy during induction phase of active LN (class III - V) in achieving primary renal response (ratio of urinary protein to creatinine of ≤0.7 and an estimated glomerular filtration rate (eGFR)

that is no worse than 20% below the pre-flare value or ≤60 mL/min/1.73 m^2 and no rescue therapy for treatment failure) at week 104.[85, level I]

8.2 Mucocutaneous

Topical agents (corticosteroids or CNIs) and HCQ are the mainstay of treatment in CLE. Systemic corticosteroids may be considered in moderate to severe CLE or when topical treatment is insufficient or not practical.[23]

In a Cochrane systematic review of 61 RCTs with interventions for CLE showed:[86, level I]

- HCQ was more effective than placebo in achieving partial clinical response at 12 months although the difference was not significant
- HCQ was superior to placebo on reducing clinical flares at six months (RR=0.49, 95% CI 0.28 to 0.89)
- MTX was superior to placebo in achieving complete clinical response at six months (RR=3.57, 95% CI 1.63 to 7.84)
- MTX led to fewer flares compared with placebo at 12 months, however it was not significant
- no difference between AZA and ciclosporin in complete clinical response at 12 months

Based on GRADE, the body of evidence was of moderate to low quality.

8.3 Neuropsychiatry

Treatment of NPSLE is determined by the underlying pathophysiology i.e. inflammatory or thrombotic. Corticosteroids and/or immunosuppressive agents should be considered in the former, while anticoagulant/antithrombotic treatment is favoured in the latter especially when aPLs are present.[50]

As mentioned earlier in **Subchapter 6.2**, two systematic reviews showed that CYC in combination with corticosteroids was more effective compared with corticosteroids alone in NPSLE. The treatments also had a good safety profile.[68, level I; 70, level I]

Anti-epileptics and anti-psychotics may be considered as adjunct therapy when indicated.

8.4 Haematology

Haematological manifestations frequently requiring immunosuppressants in SLE include thrombocytopenia and AIHA. First-line treatment of significant lupus thrombocytopenia (platelet count below 30,000/mm^3) and AIHA consist of moderate/high doses of corticosteroids in combination with immunosuppressants (AZA, MMF or ciclosporin).[50]

8.5 Cardiorespiratory

There is limited evidence on the management of cardiorespiratory manifestations in SLE. A small retrospective cohort study on lupus myocarditis showed no significant difference with the addition of CYC to corticosteroids on intensive care unit (ICU) stay, length of hospital stay and median left ventricular ejection fraction.[87, level II-2]

- The management of organ/system specific SLE is complex and a multidisciplinary team (MDT) approach consisting of rheumatologist(s) and other relevant specialists may be considered.

9. MONITORING

Assessment and monitoring in SLE are essential as the disease is often complicated by flares of varying severity. Few guidelines provide recommendations on monitoring disease activity, disease damage and quality of life.[21; 50; 88 - 89]

The clinical manifestations of SLE may be related to disease activity, organ damage, drug toxicity and quality of life. The monitoring includes new clinical manifestations, laboratory investigations, disease activity, organ damage, co-morbidities and drug AEs.

9.1 Clinical Features

SLE can present in various clinical manifestations (refer to **Figure 1**). Thus, a thorough history and physical examination must be undertaken at each clinic visit. Any new onset or changes in clinical manifestation would require further evaluation.

9.2 Laboratory Investigations

Laboratory tests that are commonly done for monitoring are FBC, RP, LFT, acute phase reactants (ESR and CRP), complements and urinalysis.

- **Full blood count**

FBC should be assessed at every visit to detect cytopenia which is associated with SLE flare or concomitant drug treatment.

The haematological flares during monitoring of patients with SLE are indicated by the following parameters:[21; 23]

- haemolytic anaemia with reticulocytosis
- leukopenia <4000/mm^3 total on >2 occasions*
- lymphopenia <1500/mm^3 on >2 occasions*
- thrombocytopenia <100 000/mm3*

*in the absence of offending drugs

- **Biochemistry and urinalysis**

Serum albumin and creatinine provide information on the presence and prognosis of renal involvement. Urinalysis can be used to detect early renal manifestations.

Renal biopsy is indicated during monitoring of patients with SLE with the presence of these criteria:[21; 23]

- persistent proteinuria >0.5 g/day or >3+ if quantitation not performed

- cellular casts: presence of red cell, haemoglobin, granular, tubular or mixed

LFT can be deranged due to autoimmune liver disease or liver toxicity secondary to the use of immunosuppressants. For frequency of monitoring, refer to **Appendix 8**.

- **Acute phase reactants**

Monitoring of ESR and CRP can be useful to distinguish SLE flare from infection. Raised ESR with normal CRP occur in SLE flares while both ESR and CRP are elevated in infection.[21]

- **Autoantibodies and complements**

Anti-dsDNA antibodies and complements can fluctuate with disease activity. In patients with clinical features of active SLE, rising anti-dsDNA antibodies and/or falling levels of complements indicate disease flare.[21]

Other autoantibodies (e.g. ANA and ENA) have not been demonstrated to be helpful in monitoring disease activity.

Refer to **Appendix 8** for **Frequency of Monitoring Patients in SLE**.

Recommendation 9
- All patients with systemic lupus erythematosus should be monitored based on clinical and laboratory parameters.*

*Refer to **Subchapter 8.1** and **8.2**.

9.3 Co-morbidities

a. Infection

Patients with SLE are prone to infection including tuberculosis due to their immunocompromised state contributed by both disease- and treatment-related factors. This leads to higher risk of morbidity and mortality.

High disease activity, severe leukopenia and presence of renal involvement (with/without hypogammaglobulinaemia in nephrotic syndrome) contribute independently to infection in SLE.[50]

In a cross-sectional study among patients with SLE, the factors associated with bacterial, viral and fungal infections were renal involvement, treatment with CYC and accumulated dose of corticosteroids. Additional factors for bacterial and viral infection were high SLEDAI score and thrombocytopenia.[90, level III]

The prevalence of tuberculosis among SLE patients is significantly higher than the general population.[91, level II-2] Hence, there should be a high index of suspicion for active tuberculosis in SLE especially among those on immunosuppressants and high doses of corticosteroids.[5]

A prospective cohort study of patients with SLE showed CRP and procalcitonin levels were higher in infection than disease flare ($p<0.001$). Both serum biomarkers decreased after the infections resolved.[92, level II-2]

- Early detection and prompt treatment of infection is important among patients with SLE, particularly in the setting of raised CRP and procalcitonin levels.

b. Osteoporosis

Risk factors for osteoporosis in patients with SLE include corticosteroids and reduced levels of vitamin D related to the avoidance of sun exposure. Osteoporosis is assessed by measuring bone mineral density (BMD) using dual-energy x-ray absorptiometry (DXA) and fracture risk assessment tool (FRAX) in patients aged 40 - 90 years.

In a retrospective cohort study among female patients with SLE, significant factors associated with high-risk of osteoporotic fractures assessed using the FRAX with BMD were nephritis (OR=11.35, 95% CI 1.09 to 118.57) and cumulative dose of corticosteroids (OR=1.10, 95% CI 1.05 to 1.15). The same study also described low complement levels (OR=4.38, 95% CI 1.50 to 12.81), high ESR (OR=1.04, 95% CI 1.02 to 1.07) and cumulative doses of corticosteroids (OR=1.05, 95% CI 1.01 to 1.09) as significant factors associated with risk of osteoporosis assessed using the World Health Organization (WHO) criteria.[93, level II-2]

c. Cardiovascular disease

SLE is an independent risk factor for CV disease (CVD), due to both traditional and disease-related risk factors.

In a large systematic review, the most frequently and consistently reported predictors of CV events in SLE patients were:94, level II-2

- male gender (OR=6.2, 95% CI 1.49 to 25)
- family history of cardiac disease (OR=3.6, 95% CI 1.15 to 11.32)
- neurological disorders (OR=5.2, 95% CI 2.0 to 13.9)
- dyslipidaemia (OR=3.9, 95% CI 1.57 to 9.71)
- hypertension (OR=3.5, 95% CI 1.65 to 7.54)
- presence of anti-phospholipid antibodies (OR=5.0, 95% CI 3.28 to 7.78)

However, the quality assessment on primary studies was not reported.

- It is important to identify and manage modifiable cardiovascular risk factors in SLE patients to reduce cardiac-related morbidity and mortality.

d. Malignancy

There is an increased incidence of malignancy among patients with SLE. Evidence from two systematic reviews and one cohort study showed association of malignancy with SLE:

- Non-Hodgkin lymphomas (SIR=4.39, 95% CI 3.46 to 5.49)[95, level II-2]
- leukaemia (SIR=1.75, 95% CI 1.04 to 2.76)[95, level II-2]
- lung cancer (RR=1.75, 95% CI 1.37 to 2.24)[96, level II-2]
- stomach cancer (RR=1.34, 95% CI 1.05 to 1.72)[96, level II-2]
- bladder cancer (HR=1.92, 95% CI 1.15 to 3.21)[97, level II-2]

In light of the increased risk, cancer screening should not be overlooked in the management of SLE. However, there is no evidence that more intense cancer screening than that applied in general population had better outcomes for SLE patients. Therefore, routine cancer screening should follow local recommendations for general population.[21]

- Surveillance for malignancy is essential as part of monitoring in patients with SLE.

Recommendation 10

- Patients with systemic lupus erythematosus (SLE) should be screened for the following:
  - cardiovascular risk factors
  - osteoporosis
- Infections in patients with SLE should be identified early and treated accordingly.

9.4 Drug Adverse Events

Drugs used in the treatment of SLE may have potential AEs and require regular monitoring.

In a large systematic review of different study designs, multiple toxicities had been found to be associated with drugs used for the treatment of SLE:[98, level I]

- corticosteroids -
  - higher rate of hyperglycaemia or diabetes among patients taking high dose corticosteroids compared with comparator drug (OR=1.82, 95% CI 1.04 to 3.19)

- HCQ -
  - the incidence of retinal toxicity was only 0.95/1000 patient-years
  - majority of those with retinal toxicity were on HCQ for >5 years and most used doses of >6.5 mg/kg
- AZA -
  - incidence of leukopenia or anaemia was 5 - 20%
  - abnormal LFTs requiring discontinuation of drug in 1 - 6%
- MTX -
  - LFT abnormalities ranged at 10 - 50%
- CYC -
  - incidence of leukopenia or anaemia was 5 - 10%
  - increased incidence of cervical dysplasia in patients taking CYC compared with corticosteroids alone
- MMF -
  - incidence of haematological toxicity was 1.1 - 36.8%
- NSAIDs and salicylates -
  - most powerful predictor of gastric mucosal injury (OR=26.8, 95%CI 4.9 to 148.6)
  - reduced renal function by 58% and increased serum creatinine by 163% in patients with active LN
  - abnormal liver enzymes over 10-day period of use in 44.4% of patients treated with aspirin and 20% of patients treated with NSAIDs

Refer to **Appendix 7** for **Medication in SLE**.

9.5 Frequency and Interval

A summary of current guidelines for laboratory monitoring as well as an overview of laboratory abnormalities of each drug and recommendations on frequency of monitoring are provided in the **Appendix 7** and **Appendix 8**.

A prospective cohort study on patients with inactive disease of SLE showed that a clinic visit interval of 3.8 months was able to identify silent manifestations of the disease.[99, level II-2]

Refer to **Appendix 7** for the **Medication in SLE**.

10. SPECIAL CONSIDERATION

10.1 Antiphospholipid Syndrome

APS is a condition characterised by the presence of aPL in the setting of venous or arterial thrombosis and/or pregnancy morbidity (complication or loss). Definite APS fulfilling at least one clinical and one laboratory criteria of the Sapporo Classification Criteria can occur in association with other autoimmune diseases mainly SLE (secondary APS) or in its primary form (primary APS).[100] Refer to **Appendix 9** on **Sapporo Classification Criteria**.

The aPL profile determines the risk of thrombotic and obstetric events. The profile is defined according to:[100]

- aPL type
- presence of multiple (double or triple) vs single aPL
- titre (moderate to high vs low)
- persistence of aPL positivity

High-risk aPL profile refers to persistently positive medium/high titres or multiple positivity.[100] EULAR guidelines recommends that all patients with SLE should be screened at diagnosis for aPL.[23]

In patients with SLE, 15 - 20% have secondary APS. Patients with SLE who have aPL also have a higher prevalence of valve disease, thrombocytopenia, haemolytic anaemia, renal lesions, cognitive impairment as well as higher tissue and organ damage compared with those without aPL.[101 - 102, level III]

The significant protective role of low dose aspirin (LDA) as primary prophylaxis against thrombosis in patients with SLE who have aPL was shown in a meta-analysis of five cohort studies (HR ranging from 0.32 to 0.43 with adjustment of CV risk factor, aPL and HCQ use).[103, level II-2] Patients with SLE with high-risk aPL profile may receive primary prophylaxis with antiplatelet agents, especially if other atherosclerotic/thrombophilic factors are present, after considering the risk of bleeding.[23]

There is no retrievable evidence exclusively on SLE with APS. Thus, the management approach of patients with SLE who have APS (secondary prevention) should follow guidelines for primary APS. Direct oral anticoagulant (DOAC) for secondary prevention is not currently recommended for patients with SLE who have APS.[100] Management of SLE with APS is beyond the scope of this CPG and thus should be initiated in consultation with the rheumatologist.

Recommendation 11

- Patients with systemic lupus erythematosus (SLE) who have high-risk antiphospholipid antibody profile may receive primary thromboprophylaxis with low dose aspirin if there are no contraindications.
- Secondary thromboprophylaxis in patients with SLE who have antiphospholipid syndrome should be initiated in consultation with a rheumatologist.

10.2 Pregnancy

a. Pre-pregnancy care and contraception

Pre-pregnancy care is the provision of biomedical, behavioural and social health interventions to women and couples before conception. It aims at improving their health status, as well as reducing morbidity and mortality of both mother and child.

- It is important to ensure that patients with SLE who plan to get pregnant achieve the following:[104]
  - remission or low disease activity for ≥6 months
  - well-controlled blood pressure
  - eGFR >60 mL/min/1.73 m^2
  - proteinuria <1 g/day (proteinuria 2+)

Counselling on contraception is important to patients with SLE who have just started on medication. This is to ensure that patient is stable on the pregnancy-compatible medication before conception.

A meta-analysis of six cohort studies showed that maternal adverse pregnancy outcomes in SLE were pre-eclampsia, miscarriage, foetal loss, risk of caesarean delivery and still birth while foetal complication were pre-term birth, small for gestational age and low birth weight.[105, level II-2]

Associated factors of adverse pregnancy outcomes in SLE are presence of active disease, aPL positivity, abnormal uterine and umbilical artery Doppler studies, low complement and thrombocytopenia at early pregnancy.[106 - 107, level II-2]

A cross-sectional study among women with SLE found that a third of them did not receive contraception counselling when they were started on potentially teratogenic medications.[108, level III] Thus, it is crucial for women with SLE especially those in reproductive age group to receive a thorough pre-pregnancy counselling on contraception and combined care of the rheumatologist and obstetrician once they are pregnant.

Oral contraceptive and intrauterine device (IUD) have no association with thrombosis, worsening of SLEDAI score and mortality in patients with SLE.[15, level I; 109, level I] Refer to **Appendix 10** for the **Types of Contraception Recommended for Patients with SLE**.

Recommendation 12
- All women with systemic lupus erythematosus in the reproductive age should receive pre-pregnancy counselling.

b. Antenatal care

The management principles for SLE during pregnancy are as follows:
- Obstetric Care: Standard pregnancy care protocols provided by the obstetric team shall be followed.
- Rheumatological or Subspecialty Care: The rheumatologist or a subspecialty team will co-manage any disease-related complications and ensure optimal care for the patient.
- Combined Care: Effective communication and multidisciplinary care among healthcare providers co-ordinated by family medicine specialists are essential.

The management of pregnant women with SLE is tabulated below (refer to T**able 4**).

Table 4: Management of Pregnant Women With SLE

Timeline	Monitoring	Action Plan
First trimester	• Blood pressure • SLE clinical assessment • Laboratory investigation* • Foetal ultrasound to confirm intrauterine pregnancy and establish gestational age	• Start low dose aspirin • Be vigilant for disease flares • Review medication compatibility and adherence • Patients with obstetric-APS** - start prophylactic LMWH • Patients with thrombotic APS** - switch from oral anticoagulants to full dose LMWH • For active SLE: o medication adjustment o MDT discussion and shared decision-making for continuation of pregnancy in certain situations • Schedule for combined care
Second trimester	• Blood pressure • SLE clinical assessment • Laboratory investigations* with assessment for gestational diabetes and genetic screening (if applicable) • Foetal echocardiogram between 16 - 25 weeks of	• Be vigilant for disease flares • Review medication adherence • Calcium supplementation for pre-eclampsia prophylaxis if not started previously. The recommended dose is calcium carbonate 1 g BD commenced before 20 weeks gestation. • congenital heart block,

	gestation for mothers with positive anti-Ro/SSA or anti-La/SSB by feto-maternal specialist • Ultrasound to evaluate foetal anatomy, foetal growth and placental insufficiency	co-management with feto-maternal specialist is required
Third trimester	• Blood pressure • SLE clinical assessment • Laboratory investigations* • Regular ultrasound to evaluate foetal growth, adequacy of amniotic fluid and placental insufficiency	• Be vigilant for disease flares • Review medication adherence • Review preparations for labour and delivery • Avoid NSAIDs
Post-partum and lactation	• Blood pressure • SLE clinical assessment • Laboratory investigations*	• Be vigilant for disease flares • For APS - continue LMWH for 6 weeks • Switch to lactation compatible medications if breastfeeding is desired • For prednisolone ≥40 mg/day, delay breastfeeding at least four hours after consumption • Refer neonate to paediatrician to rule out neonatal lupus • Advise regarding contraception***

Notes:
*Laboratory investigations to be included: full blood count (FBC), renal profile (RP), liver function test (LFT), urinalysis and morning urine protein to creatinine ratio (UPCR), anti-double stranded DNA (anti-dsDNA) antibodies, complement levels (C3 and C4), serum uric acid.
Refer to **Appendix 9 for **Sapporo Classification Criteria**
***Refer to **Appendix 10** for T**ypes of Contraception Recommended for Patients With SLE**
Abbreviations: APS = antiphospholipid syndrome; BD = twice daily; HCQ = hydroxychloroquine; g = gram; LMWH = low molecular weight heparin; MDT = multidisciplinary team; NSAIDS = nonsteroidal anti-inflammatory drugs; SLE = systemic lupus erythematosus

Adapted from: Dao KH, Bermas BL. Systemic Lupus Erythematosus Management in Pregnancy. Int J Womens Health. 2022;14:199-211.

- **Medication**

Medications in SLE patients with pregnancy should be adjusted and reviewed accordingly even prior to conception. The goal of treatment is to prevent SLE flare and ensure the best safety profile during pregnancy.

HCQ use in pregnancy is safe and effective in SLE. A systematic review and an RCT support its use in reducing disease activity and Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) score.[110, level I; 111, level II-2] One meta-analysis and two cohort

studies also showed no significant association of HCQ use and foetal loss, pre-term delivery and pre-eclampsia.[111, level II-2; 112, level II-2; 113, level II-2]

Corticosteroids is also the cornerstone treatment in pregnancy. However, its dose should be reduced to lowest effective dose prior to conception to ensure its safety in pregnancy. In a meta-analysis of overall good quality primary studies, the use of corticosteroids >7.5 mg/day was associated with risk of pre-term delivery, small gestational age and foetal loss.[114, level II-2] Nevertheless, CPG DG opines that for mild to moderate SLE flare, a dose increment may be considered but then tapered accordingly.

HCQ, AZA, CNIs and low dose corticosteroids are safe to be used throughout pregnancy as recommended by guidelines.[46]

ACR recommends the initiation of LDA in SLE patients at the beginning of first trimester in order to preclude or delay the onset of gestational hypertension in pregnancy.[46] LDA is also safe in pregnancy as it shows no significant foetal outcomes e.g. small gestational age, intrauterine growth restriction or preterm delivery in patients taking LDA compared with those without LDA.[115, level II-2]

Refer to **Appendix 7** for use of SLE medication in pregnancy and lactation.

- The CPG DG opines that all SLE patients who are pregnant especially those with positive aPL should be referred to the rheumatologist at antenatal booking.
- All pregnant SLE patients should be under combined care of rheumatologist/physician, feto-maternal specialist/obstetrician and family medicine specialist.
- Calcium supplementation is essential in pregnant SLE patients for pre-eclampsia prophylaxis.

Recommendation 13

- The following medications should be continued in systemic lupus erythematosus (SLE) with pregnancy:
  - hydroxychloroquine
  - azathioprine
  - calcineurin inhibitors
  - low dose corticosteroids
- Low dose aspirin should be initiated in all pregnant SLE patients unless intolerance or contraindicated.

10.3 Lactation

Breastfeeding is encouraged and not contraindicated in patients with SLE as long as the disease control can be maintained with medication compatible with lactation. Refer to **Appendix 7** on **Medication in SLE** for medication compatible with lactation.

10.4 Adolescents

SLE is diagnosed during childhood in 15 to 20% of patients.[116, level III] A co-ordinated transition from paediatric to adult care providers starting during adolescence has been recommended to ensure the patients' physical, psychosocial, educational and vocational needs are met.[117]

Two observational studies showed that a structured transition programme or clinic was important to improve long-term outcomes. In a cross-sectional study on childhood-onset SLE, patients who experienced difficulty during transition compared with those without difficulty were more likely to report 'poor overall control' of symptoms (p=0.03) and involvement of multiple organ systems (p=0.05). Patients who were directly referred to an adult physician by a paediatric rheumatologist rather than self-referred reported 'well controlled' overall symptoms (p=0.01) and lower hospitalisation (p=0.04).[118, level III] Another single-centre, pre-post study on childhood-onset SLE cohort with no formal transition programme showed that 72% were lost to follow-up.[119, level II-3]

Two programmes described in a systematic review of transitional care in rheumatology showed improvements in the following outcomes:[120, level II-3]

- health-related quality of life, arthritis-related knowledge and satisfaction with rheumatic care in adolescents and parents
- vocational readiness
- physical, psychosocial and disease-specific health status

Young people with rheumatic and musculoskeletal diseases which include SLE should have access to co-ordinated transitional care, delivered through partnership with healthcare professionals. The transition process should start as early as possible.[117]

Recommendation 14

- A structured transition programme may be implemented to facilitate transfer of care from paediatric to adult health care providers during adolescence in patients with childhood-onset systemic lupus erythematosus.

10.5 Vaccination

Vaccination is an important strategy in patients with SLE as they are susceptible to infection due to the disease itself, immunosuppressive therapy and presence of co-morbidities. EULAR recommends annual assessment of vaccination status of patients with autoimmune inflammatory rheumatic diseases and administration of vaccines during quiescent disease.[121]

The evidence for effectiveness based on immunogenicity and safety for vaccines in SLE patients are provided in the table below (refer to **Table 5**).

Table 5: Effectiveness and safety of vaccines in SLE patients

Non-live vaccines		
Vaccine	**Effectiveness**	**Safety**
Pneumococcal [122, level I]	A systematic review noted increase of IgM antibody titre in patients with SLE vs controls. Immunosuppressive therapy (except belimumab) resulted in lower seroconversion rates (43 - 77% in patients on immunosuppression vs 52 - 90% in those without immunosuppression).	No serious AEs were noted while SLE flares were rarely reported. Disease activity scores remained stable before and after immunisation.
Influenza [123, level II-2]	A meta-analysis showed moderate immunogenicity in SLE patients vs healthy controls.	A meta-analysis showed moderate immunogenicity in SLE patients vs healthy controls.
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	A systematic review with meta-analysis of patients with immune mediated inflammatory diseases including SLE patients found that seroconversion rates were:[124, level III] • higher after a two-dose regimen vs single dose of messenger RNA (mRNA) vaccine • lower than healthy controls • lower among those exposed to anti-CD20 therapy vs other immunosuppressants Humoral response was similar to general population after the third dose.[125, level II-2]	A cohort study showed that SLE disease activity was not affected. Vaccine-breakthrough infections, mainly with Omicron variant, were mild and did not require hospitalisation.[125, level II-2]
Human Papillomavirus (HPV)	One cohort study[126, level II-2] and one pre-post study[127, level II-3] showed that the vaccine was generally immunogenic:	Mild vaccine site reactions occurred in 62% of patients. No SLE flares were reported.[127, level II-3]

	• seroconversion was 100% for those seronegative at baseline[127, level II-3] • high rate of immunogenicity was retained at five years in stable patients[126, level II-2]	
Live vaccines		
Herpes Zoster (HZ)[128, level I]	The vaccine induces humoral and cell-mediated response in stable SLE patients not receiving intensive immunosuppressive therapies.	Safe and well-tolerated in stable patients not receiving intensive immunosuppression. No differences noted in AEs except for injection site reactions in vaccine-treated patients vs those on placebo. Low number of SLE flares were noted in both groups.

- Pneumococcal, influenza, SARS-CoV-2 and HPV vaccines are advisable to be given to patients with SLE.
- HZ vaccine is potentially beneficial in patients with SLE.

Recommendation 15
- Vaccination status and indications for further vaccinations of patients with systemic lupus erythematosus (SLE) should be assessed yearly.
- Vaccinations should preferably be administered prior to commencement of immunosuppressants or during remission/low disease activity of SLE.

11. REFERRAL

Timely referral to or consultation with rheumatologists is of utmost importance for confirmation of diagnosis and early initiation of treatment for SLE. Even though rheumatologists are the specialists who primarily care for patients with SLE, co-management with specialists in other disciplines (e.g. primary care physicians, nephrologists and haematologists) is equally important.

Indications for referral to rheumatologist includes to confirm diagnosis, assess disease activity and severity, provide general disease management, manage organ involvement or life-threatening disease and manage/prevent treatment toxicities. Other specific circumstances that require referral include APS, pregnancy and perioperative management.[129, level III]

For moderate to severe organ involvement, patients with SLE will require multidisciplinary care involving various subspecialties.

Indications for urgent referral are as listed below:

- for patients not diagnosed with SLE yet -
  - clinical suspicion of SLE with major or multisystem organ involvement
- for patients diagnosed with SLE -
  - disease flare of major organ or multisystem organ involvement
  - pregnancy (at booking)
  - severe infection

Recommendation 16

- All cases with clinical suspicion of systemic lupus erythematosus should be promptly referred to rheumatologists for confirmation of the diagnosis and further management.

12. IMPLEMENTING THE GUIDELINES

Implementation of this CPG is important as it helps in providing quality healthcare services based on the best and most recent available evidence applied to local scenario and expertise. Various factors and resource implications should be considered for the success of the uptake in the CPG recommendations.

12.1 Facilitating and Limiting Factors

The facilitating factors in implementing the CPG are:

i) availability of CPG to healthcare providers (hardcopies and softcopies)
ii) conferences and updates on management of SLE including those involving professional bodies (e.g. Malaysian Society of Rheumatology)
iii) Key Performance Indicator on Rheumatology Services monitored by MoH (i.e. number of newly presented SLE patients prescribed HCQ in the Rheumatology Outpatient Clinic)
iv) public awareness campaigns on SLE (e.g. World Lupus Day in collaboration with Malaysian SLE Association)

Limiting factors in the CPG implementation include:

i) different levels of care and wide variation in practice due to expertise, facilities and financial constraints
ii) limited awareness and knowledge in management of SLE among healthcare providers
iii) lack of awareness of the disease and its management by the public
iv) no local SLE registry

12.2 Potential Resource Implications

Early diagnosis of SLE may be difficult to establish as the presentations are non-specific and it is even more challenging with the presence of SLE mimickers. Besides that, the supporting relevant investigations may not be easily accessible in the public primary care especially in remote areas. The confirmation of the diagnosis and its assessment requires the specialists' expert opinion especially the rheumatologists, where the service is limited nationwide. Thus, this CPG serves as a guide for early disease recognition and referral. There is a compelling need to increase awareness and knowledge on the evidence-based management of SLE by ensuring widespread distribution of the CPG and reinforcing related training to the healthcare providers.

Treatment of SLE can be a daunting task particularly in patients with severe disease and co-morbidities. The assessment of disease severity

of SLE is thus important in deciding the best management approach as inadequate treatment may lead to significant morbidity and mortality. Heterogeneity of disease manifestation warrants MDT involvement. Based on the recommendations in the CPG, the need for specialised care and certain expensive medications has resource implications that need to be addressed in the management of SLE.

In line with the key recommendations in this CPG, the following is proposed as clinical audit indicator for quality management of SLE:

$$\text{Percentage of newly diagnosed SLE patients prescribed HCQ*} = \frac{\text{Number of newly diagnosed SLE patients prescribed HCQ in a period}}{\text{Total number of newly diagnosed SLE patients in the same period}} \times 100\%$$

*Target of 90%

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the safe and effective pharmacological treatments in SLE?

- Hydroxychloroquine

1. LUPUS ERYTHEMATOSUS, SYSTEMIC/
2. (systemic adj2 lupus erythematosus*).tw.
3. sle.tw.
4. 1 or 2 or 3
5. HYDROXYCHLOROQUINE/
6. hydroxychloroquine.tw.
7. hydroxychloroquine sulfate.tw.
8. oxychloroquine.tw.
9. plaquenil.tw.
10. 5 or 6 or 7 or 8 or 9
11. 4 and 10
12. limit 11 to (english language and humans and yr=”2009 -Current”)
13. limit 12 to “systematic review”

Appendix 2

CLINICAL QUESTIONS

1. **Diagnosis and assessment**
   - What are the risk factors for SLE?
   - What are the accurate investigations to diagnose and assess SLE?
   - What are the classification criteria for SLE?
2. **Treatment**
   - What are the principles of treatment in SLE?
   - What are the safe and effective non-pharmacological treatments in SLE?
     - Patient education
     - Sun protection
     - Nurse-led care
   - What are the safe and effective pharmacological treatments in SLE?
     - Analgesics
     - Corticosteroids
     - Hydroxychloroquine and other antimalarial agents
     - Immunosuppressive agents
     - Biologics
     - Intravenous immunoglobulin
     - Plasma exchange
   - What are the safe and effective alternative and complementary medicine in SLE?
   - What are the safe and effective organ system-specific treatments in SLE?
     - Mucocutaneous
     - Musculoskeletal
     - Haematological
     - Neuropsychiatric
     - Cardio-respiratory
     - Renal
3. **Monitoring**
   - What are the effective and safe monitoring in SLE?
     - Frequency and interval
     - Parameters
     - Co-morbidities
       - Cardiovascular
       - Infection
       - Osteoporosis
       - Malignancy
     - Drug adverse events and complications

4. **Special consideration**
    - What are the effective and safe management for SLE in the following situations/groups:
        - APS (Antiphospholipid syndrome)
        - Pregnancy
            - Pre-pregnancy counseling
            - Contraception
            - Combined care
            - Lactation
        - Adolescents
        - Vaccination
5. **Referral**
    - What are the referral criteria for SLE?
        - primary to secondary/tertiary
        - inter-subspecialty
        - urgent referral (red flags)

Appendix 3

2012 SLICC CLASSIFICATION CRITERIA FOR SLE

Clinical Criteria
1. Acute Cutaneous Lupus Including lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash *in the absence of dermatomyositis* **OR subacute cutaneous lupus** (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with post-inflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus Including classic discoid rash (localized (above the neck) or generalized (above and below the neck)), hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chillblains lupus, discoid lupus/lichen planus overlap
3. Oral ulcers Palate, buccal, tongue **OR nasal ulcers** *in the absence of other causes, such as vasculitis, Behcet's disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis, and acidic foods*
4. Nonscarring alopecia *Diffuse thinning or hair fragility with visible broken hairs in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia*
5. Synovitis Involving 2 or more joints, characterized by swelling or effusion **OR** tenderness in 2 or more joints and at least 30 minutes of morning stiffness
6. Serositis Typical pleurisy for more than 1 day **OR** pleural effusions **OR** pleural rub Typical pericardial pain for more than 1 day (pain with recumbency improved by sitting forward) **OR** pericardial effusion **OR** pericardial rub **OR** pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, or Dressler's pericarditis

7. Renal Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours **OR** red blood cell casts
Clinical Criteria
8. Neurologic Seizures, psychosis, mononeuritis multiplex *in the absence of other known causes such as primary vasculitis*, myelitis, peripheral or cranial neuropathy *in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus*, acute confusional state *in the absence of other causes, including toxic/metabolic, uremia, drugs*
9. Haemolytic anaemia
10. Leukopenia or lymphopenia Leukopenia: <4,000/mm^3 at least once *in the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension* **OR** Lymphopenia <1,000/mm^3 at least once *in the absence of other known causes such as corticosteroids, drugs, and infection*
11. Thrombocytopenia Thrombocytopenia <100,000/mm^3) at least once *in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura*

Immunologic Criteria
1. ANA level above laboratory reference range
2. Anti-dsDNA antibody level above laboratory reference range (or 2-fold the reference range if tested by ELISA)
3. Anti-Sm Presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody Positive test result for lupus anticoagulant, false-positive test result for rapid plasma regain, medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM), positive test result for anti-β2-glycoprotein 1 (IgA, IgG, or IgM)
5. Low complement Low C3, low C4, low CH50
6. Direct Coombs' test *in the absence of hemolytic anemia*

Source: Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-2686.

Appendix 4

2019 EULAR/ACR CLASSIFICATION CRITERIA FOR SLE

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on Hep-2 cells or an equivalent positive test (ever)

If absent, do not classify as SLE
If present, apply additive criteria

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE
Occurrence of a criterion on at least one occasion is sufficient
SLE classification requires at least one clinical criterion and ≥10 points
Criteria need not occur simultaneously
With each domain, only the highest weighted criterion is counted toward the total score§

Clinical domains and criteria	Weight	Immunological domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Haematologic		Anti-β2GP1 antibodies OR	2
Leukopenia	3	Lupus anticoagulant	
Thrombocytopenia	4	***Complement proteins***	
Autoimmune haemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	6
Seizure	5	Anti-Smith antibody	
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5 g/24 h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		
TOTAL SCORE			

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled

*In an assay with ≥90% specificity against relevant disease controls
§Additional criteria items within the same domain will not be counted.
ANA = antinuclear antibodies; Anti-β2GP1 = anti-beta-2-glycoprotein 1; Anti-dsDNA = anti-double stranded deoxyribonucleic acid; C3 = complement 3; C4 = complement 4
g = gram; h = hour; SLE = systemic lupus erythematosus

Source: Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019;71(9):1400-1412.

Appendix 5

SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX 2000 (SLEDAI-2K)

Study No.: _____ Patient Name: _____Visit Date: _____

(Enter weight in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 10 days.)

Weight	SLEDAI Score	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Pscyhosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥2 joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.

Weight	SLEDAI Score	Descriptor	Definition
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/2 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal range for testing laboratory.
2	_____	Increases DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38°C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / x109/L, exclude drug causes.
1	_____	Leukopenia	<3,000 white blood cells / x109/L, exclude drug causes.
TOTAL SLEDAI SCORE			

Source: Gladman DD, Ibañez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol. 2002;29(2):288-291.

Appendix 6

BRITISH ISLES LUPUS ACTIVITY GROUP (BILAG) INDEX - 2004

Centre: Date: Initials/Hosp No:

- **Only record manifestations/items due to SLE Disease Activity**
- **Assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)**
- **TO BE USED WITH THE GLOSSARY**

Record: **ND** **Not Done**
0 **Not present**
1 **Improving**
2 **Same**
3 **Worse**
4 **New**
Yes/No OR Value (where indicated)
***Y/N** **Confirm this is due to SLE activity (Yes/No)**

CONSTITUTIONAL

1. Pyrexia - documented > 37.5ºC ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS

5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/ thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC

19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )

NEUROPSYCHIATRIC cont.

29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL

39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/ Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/ Myalgia ( )

CARDIORESPIRATORY

44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/ vasculitis ( )
52. Interstitial alveolitis/ pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL

56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC

65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL

78. Systolic blood pressure (mm Hg) value ( ) **Y/N***
79. Diastolic blood pressure (mm Hg) value ( ) **Y/N***
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) **Y/N***
82. Urine albumin-creatinine ratio mg/mmol ( ) **Y/N***

RENAL cont.

82. Urine protein-creatinine ratio mg/mmol ( ) **Y/N***
83. 24 hour urine protein (g) value ( ) **Y/N***
84. Nephrotic syndrome Yes/No ( )
85. Creatinine (plasma/serum) µmol/l ( ) **Y/N***
86. GFR (calculated) ml/min/1.73 m^2 ( ) **Y/N***
87. Active urinary sediment Yes/No ( )
88. Active nephritis Yes/No ( )

HAEMATOLOGICAL

90. Haemoglobin (g/dl) value ( ) **Y/N***
91. Total white cell count (x 10^9/l) value ( ) **Y/N***
92. Neutrophils (x 10^9/l) value ( ) **Y/N***
93. Lymphocytes (x 10^9/l) value ( ) **Y/N***
94. Platelets (x 10^9/l) value ( ) **Y/N***
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Weight (kg):	**Serum urea (mmol/l):**
African ancestry: Yes / No	**Serum albumin (d/l):**

Source: Yee CS, Cresswell L, Farewell V, et al. Numerical scoring for the BILAG-2004 index. Rheumatology. 2010;49:1665-1669.

MEDICATION IN SLE

Drugs	Recommended Dosages	Common Adverse Events	Monitoring and Frequency	Pregnancy and Lactation
Corticosteroids				
Prednisolone	Low dose: <7.5 mg OD PO Intermediate dose: 7.5 - 30 mg OD PO High dose: >30 mg OD PO	• Elevated blood pressure • Infection • Acne • Hyperglycaemia • Dyslipidaemia • Osteoporosis • Muscle weakness • Fluid retention • Weight gain	Glucose levels 3 - 6-monthly Total cholesterol 6 - 12-monthly Bone mineral density when indicated Infection	Pregnancy Can be continued at lowest effective dose Lactation Compatible
Methylprednisolone	IV infusion ≥250 mg/day for 1 - 3 days (pulse)			
Hydrocortisone	IV 50 - 100 mg TDS/QID			
Antimalarial				
Hydroxychloroquine	200 - 400 mg OD PO (5 mg/kg/day actual body weight) Renal adjustment: CrCl (mL/min 1.73m²) / Dose adjustment ≥60 / None 30 - 59 / 150 mg OD 10 - 29 / 50 - 100 mg OD <10 / 50 - 100 mg OD	• Skin hyperpigmentation • Prolonged QT interval • Abnormal FBC • Abnormal liver enzyme • Retinal toxicity	Ophthalmologic assessment at baseline, then: • yearly in the presence of known retinopathy risk factors • after 5 years and yearly thereafter in the absence of retinopathy risk factors FBC, LFT at initiation of treatment and when indicated	Pregnancy Compatible Lactation Compatible

<table>
<tr><th>Drugs</th><th>Recommended Dosages</th><th>Common Adverse Events</th><th>Monitoring and Frequency</th><th>Pregnancy and Lactation</th></tr>
<tr><td colspan="5">Immunosuppressants</td></tr>
<tr><td>Azathioprine</td><td>50 - 250 mg as a single dose or divided into 2 doses PO
(1 - 2.5 mg/kg/day)</td><td>• GI intolerance
• Abnormal FBC
• Abnormal liver enzyme</td><td>FBC, LFT at initiation of treatment, at 2 weeks and when indicated

Infection</td><td><u>Pregnancy</u>
Compatible

<u>Lactation</u>
Compatible</td></tr>
<tr><td>Methotrexate</td><td>7.5 - 25 mg weekly PO

Renal adjustment:<table><tr><th>CrCl (mL/min/ 1.73m^2)</th><th>Dose adjustment</th></tr><tr><td>≥60</td><td>None</td></tr><tr><td>30 - 59</td><td>Reduce 50%</td></tr><tr><td><30</td><td>Contra-indicated</td></tr></table></td><td>• Abnormal liver enzyme
• Abnormal FBC
• GI intolerance
• Alopecia
• Mucositis
• Photosensitivity, rash
• Interstitial pneumonia (acute/chronic)
• Renal impairment</td><td>FBC, LFT, RP at 2 - 4-weekly for the first 3 months or at every dose increase, then 3-monthly

Infection

Folic acid 5 mg weekly PO (minimum) to ameliorate AEs</td><td><u>Pregnancy</u>
• Contraindicated
• Stop at least 3 months prior to conception

<u>Lactation</u>
Contraindicated</td></tr>
<tr><td>Ciclosporin</td><td>2.5 - 4 mg/kg/day in 2 divided doses PO</td><td>• Elevated blood pressure
• Tremor
• Hirsutism/hypertrichosis
• Renal impairment
• Gum hypertrophy
• Abnormal liver enzyme
• GI symptoms
• Anaemia
• Paraesthesia</td><td>Blood pressure

FBC, RP and LFT at initiation of treatment, at 2 weeks and when indicated

Infection</td><td><u>Pregnancy</u>
Compatible

<u>Lactation</u>
Compatible</td></tr>
</table>

Drugs	Recommended Dosages	Common Adverse Events	Monitoring and Frequency	Pregnancy and Lactation
Tacrolimus	1 - 3 mg/day in 2 divided doses PO (0.1 - 0.15 mg/kg/day) *need to assess drug levels (TDM)	• GI intolerance • Peripheral oedema • Alopecia • Abnormal FBC • Renal impairment	RP at initiation of treatment, at 2 weeks and when indicated Infection	Pregnancy Compatible Lactation Compatible
Cyclophosphamide	50 - 100 mg OD PO **NIH regimen:** IV infusion 0.5 - 1 g/m^2 monthly for 6 cycles **Euro-Lupus regimen:** IV infusion 500 mg 2-weekly for 6 cycles	• GI intolerance • Alopecia • Abnormal FBC	FBC, LFT at initiation of treatment, at 2 weeks and when indicated UFEME at initiation and when indicated Malignancy, infection and haemorrhagic cystitis Caution in patients of reproductive age due to possible gonadal dysfunction	Pregnancy Contraindicated Lactation Contraindicated
Leflunomide	10 - 20 mg OD PO	• Alopecia • Abnormal FBC • Abnormal liver enzyme • Elevated blood pressure	FBC, LFT at 2 - 4-weekly for the first 3 months or at every dose increase, then 3-monthly Blood pressure Infection	Pregnancy • Contraindicated • A washout procedure should be completed pre-conception Lactation Contraindicated
Mycophenolate mofetil	1 - 1.5 g BD PO	• GI intolerance • Abnormal FBC	FBC, LFT 2-weekly until stable then at least 3-monthly Infection	Pregnancy • Contraindicated • Stop at least 6 weeks prior to conception Lactation Contraindicated

Drugs	Recommended Dosages	Common Adverse Events	Monitoring and Frequency	Pregnancy and Lactation
		Biologics		
Belimumab	IV infusion 10 mg/kg 4-weekly	• GI intolerance • Infusion-related reaction • Infection	FBC, LFT at initiation of treatment, at 2 weeks and when indicated Depression or suicidal ideation Infection	Pregnancy Limited data Lactation Compatible
Rituximab	IV infusion 1000 mg on day 1 and day 15 May be repeated 6-monthly Premedication 30 minutes before infusion: • IV methylprednisolone 100 mg • IV antihistamine • Paracetamol PO	• Peripheral oedema • Pruritus • Rash • GI intolerance • Abnormal FBC • Infection • Infusion-related reaction • Low IgG/IgA/IgM	FBC at initiation of treatment, at 2 weeks and when indicated IgG, IgA, IgM when indicated Caution in patients with hepatitis B infection, history of infusion reaction, progressive multifocal leukoencephalopathy	Pregnancy Can be used in exceptional cases in early gestation. If used at later stages of pregnancy, clinician should be aware of risk of B cell depletion and other cytopenias in the neonate Lactation Contraindicated
Anifrolumab	IV infusion 300 mg 4-weekly	• Infection • Herpes zoster • Bronchitis • Infusion-related reaction	FBC, LFT at initiation of treatment, at 2 weeks and when indicated Infection	Pregnancy Limited data Lactation Contraindicated

Drugs	Recommended Dosages	Common Adverse Events	Monitoring and Frequency	Pregnancy and Lactation
Nonsteroidal anti-inflammatory drugs				
Ibuprofen	400 - 800 mg TDS PO	• GI intolerance • Rash • Peripheral oedema • Abnormal liver enzyme • Elevated blood pressure • Renal impairment	FBC, LFT, RP at initiation of treatment and when indicated Caution in patients with GI bleeding, liver disease, kidney disease or hypertension	Pregnancy • NSAIDs can be used in first and second trimester only • COX-2 inhibitors are not preferred Lactation Generally, all are compatible except etoricoxib
Diclofenac	50 mg TDS PO			
Naproxen	250 - 500 mg BD PO (equivalent to 275 - 550 mg naproxen sodium)			
Mefenamic acid	250 - 500 mg TDS PO			
Meloxicam	7.5 - 15 mg OD PO			
Etoricoxib	60 - 90 mg OD PO			
Celecoxib	200 mg OD or BD PO			
Others				
Human intravenous immunoglobulin	IV infusion 0.4 g/kg/day for 5 days or IV infusion 1 g/kg/day for 2 days	• Elevated blood pressure • GI intolerance • Infusion-related reaction • Thromboembolism	Blood pressure Allergic reactions	Pregnancy Compatible Lactation Compatible

BD = bis in die (twice a day); COX-2 = cyclooxygenase-2; CrCl = creatinine clearance; FBC = full blood count; g = gram; GI = gastrointestinal; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IV = intravenous; kg = kilogram; LFT = liver function test; m^2 = square metre; mg = milligram; min = minute; mL = millilitre; NIH = National Institute of Health; OD = once a day; PO = per os (by oral); QID = quarter in die (four times a day); RP = renal profile; TDM = therapeutic drug monitoring; TDS = ter die sumendum (three times a day); UFEME = urine full examination and microscopic examination

Source:

1. Adams K, Bombardier C, van der Heijde DM. Safety of pain therapy during pregnancy and lactation in patients with inflammatory arthritis: a systematic literature review. J Rheumatol Suppl. 2012;90:59-61.
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a pregnancy registry and postmarketing reports. Ann Rheum Dis. 2023;82(2):217-225.
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Appendix 8

FREQUENCY OF MONITORING PATIENTS WITH SLE

Assessments	At first visit	Patients with active disease should be reviewed at least every 1 - 3 months	Patients with stable/ low disease activity should be reviewed every 6 - 12 months
Clinical			
History	✓	✓	✓
Vital signs (blood pressure, heart rate, weight)	✓	✓	✓
Clinical examination	✓	✓	✓
Drug review	✓	✓	✓
Blood tests			
Full blood count	✓	✓	✓
Renal profile	✓	✓	✓
Liver function test	✓	✓	✓
CRP	✓	✓[a]	✓[a]
ESR	✓	✓	✓
Bone profile (calcium, phosphate, ALP)	✓[a]	✓[a]	✓[a]
Vitamin D3	✓[a]	-	✓[a]
Immunology/serology			
ANA	✓	-	-
Anti-dsDNA	✓	✓[a]	✓[a]
C3/C4 levels	✓	✓	✓[a]
aPL (LA, aCL, aβ2GPI)	✓	✓[a]	✓[a,p]
ENA (anti-Ro/La, anti-RNP, anti-Sm antibodies)	✓	✓[a]	✓[a,p]
Immunoglobulin A, G, M	✓[a]	✓[a]	✓[a]
Direct Coombs' test	✓	✓[a]	✓[a]
Urine			
UFEME	✓	✓	✓
Urine random protein: creatinine ratio OR 24-hour urine protein	✓[a]	✓[a]	✓[a]
Other investigation			
Culture	✓[a]	✓[a]	✓[a]
Biopsy (e.g. skin, kidney)	✓[a]	✓[a]	✓[a]
Neurophysiology (e.g. nerve conduction study, EMG)	✓[a]	✓[a]	✓[a]
ECG	✓[a]	✓[a]	✓[a]
Echocardiogram	✓[a]	✓[a]	✓[a]
Imaging			
Chest X-ray	✓[a]	✓[a]	✓[a]
Others (US, CT, MRI)	✓[a]	✓[a]	✓[a]

Assessments	At first visit	Patients with active disease should be reviewed at least every 1 - 3 months	Patients with stable/ low disease activity should be reviewed every 6 - 12 months
Modifiable cardiovascular risk factors			
Hypertension	✓	✓	✓
Dyslipidaemia	✓	✓[a]	✓[a]
Diabetes mellitus	✓	✓	✓
High BMI	✓	✓	✓
Smoking/vaping	✓	✓	✓

✓ = indicated; ✓[a] = when indicated; ✓[a,p] = when indicated during pregnancy; - = not indicated; aβ2GP1 = anti-beta-2-glycoprotein 1 antibodies; aCL = anticardiolipin antibodies; ALP = alkaline phosphatase; ANA = antinuclear antibody; anti-dsDNA = anti-double stranded deoxyribonucleic acid; anti-RNP = antibodies to ribonucleoprotein; anti-Sm antibodies = anti-Smith antibodies; aPL = antiphospholipid antibody; BMI = body-mass index; C3 = complement 3, C4 = complement 4, CRP = C-reactive protein; CT = computerised tomography; ECG = electrocardiogram; EMG = electromyogram; ENA = extractable nuclear antigen; ESR = erythrocyte sedimentation rate; LA = lupus anticoagulants; MRI = magnetic resonance imaging; UFEME = urine full examination and microscopic examination; US = ultrasound

Adapted from: Gordon C, Amissah-Arthur MB, Gayed M, et al. The British Society for Rheumatology guidelines for the management of systemic lupus erythematosus in adults. Rheumatology. 2018;57(1);e1-e45.

Appendix 9

SAPPORO CLASSIFICATION CRITERIA (REVISED CLASSIFICATION CRITERIA FOR THE ANTIPHOSPHOLIPID SYNDROME)

Antiphospholipid syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met*

Clinical criteria

1. Vascular thrombosis†

One or more clinical episodes‡ of arterial, venous or small vessel thrombosis§, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity
   (a) One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus, or
   (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognised features of placental insufficiency¶, or
   (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and, paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b or c above.

Laboratory criteria**

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).
2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotypes in serum or plasma, present in medium or high titre (i.e. >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA.

3. Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titre >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA, according to recommended procedures.

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*Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestations.

†Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognised, according to: (a) the presence, and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include: age (>55 in men and >65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body-mass index ≥30 kg/m^2, microalbuminuria, estimated GFR <60 mL/min), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilisation and surgery. Thus, patient who fulfil criteria should be stratified according to contributing causes of thrombosis.

‡A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.

§Superficial venous thrombosis is not included in the clinical criteria.

¶Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring foetal surveillance test(s), e.g. a non-reactive non-stress test, suggestive of foetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of foetal hypoxaemia, e.g. absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.

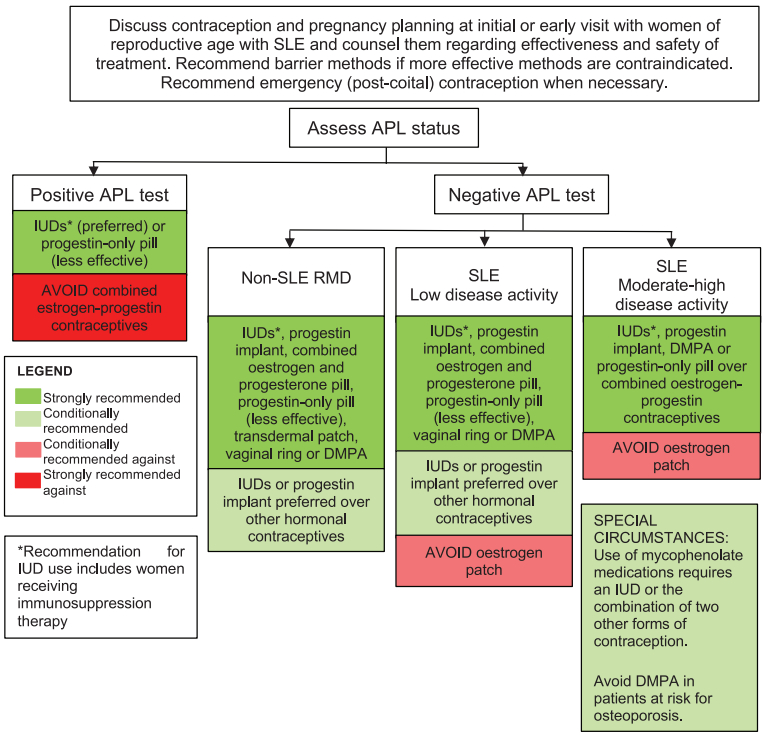
**Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present along; IIb, aCL antibody present alone; IIc, anti-beta-2-glycoprotein 1 antibody present alone.

Source: Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4:295-306.

Appendix 10

RECOMMENDATIONS ON TYPES OF CONTRACEPTION FOR PATIENTS WITH SLE

i) ACR-2020



aPL = antiphospholipid antibody (persistent moderate-to-high-titre anticardiolipin or anti-β2-glycoprotein 1 antibody or persistent positive LA); IUDs = intrauterine devices (copper or progestin); SLE = systemic lupus erythematosus; DMPA = depot medroxyprogesterone acetate

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

ii) WHO-2015

SUMMARY TABLE (MECC categories)									
	COC/P/CVR	CIC	POP	DMPA/NET-EN		LNG/ETG IMPLANTS	CU-IUD		LNG-IUD
				I	C		I	C	
a. Positive (or unknown) antiphospholipid antibodies	4	4	3	3	3	3	1	1	3
b. Severe thrombocytopenia	2	2	2	3	2	2	3	2	2
c. Immunosuppressive treatment	2	2	2	2	2	2	2	1	2
d. None of the above	2	2	2	2	2	2	1	1	2

MECC categories for contraceptive eligibility	
1	A condition for which there is no restriction for the use of the contraceptive method.
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks.
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method.
4	A condition which represents an unacceptable health risk if the contraceptive method is used.

C = continuation; CIC = combined injectable contraceptive; COC = combined oral contraceptive (pill); CU-IUD = copper-bearing intrauterine device; CVR = combined contraceptive vaginal ring; DMPA = depot medroxyprogesterone acetate; ETG = etonogestrel; I = initiation; LNG = levonorgestrel; LNG-IUD = levonorgestrel-releasing intrauterine device; NET-EN = norethisterone enanthate; P = combined contraceptive patch; POP = progestogen-only pill

Source: WHO. Medical eligibility criteria for contraceptive use (Fifth edition). Geneva; WHO: 2015.

LIST OF ABBREVIATIONS

24hUP	24-hour urine protein
aCL	anticardiolipin antibodies
ACR	American College of Rheumatology
AE	adverse event
AGREE	Appraisal of Guidelines for Research and Evaluation
AIHA	autoimmune haemolytic anaemia
ALMS	Aspreva Lupus Management Study
ALP	alkaline phosphatase
ANA	antinuclear antibodies
anti-β2GP1	anti-beta-2-glycoprotein 1
anti-dsDNA	anti-double stranded deoxyribonucleic acid
anti-RNP	antibodies to ribonucleoprotein
anti-Sm	anti-Smith
anti-SSA	anti-Sjögren's-syndrome-related antigen A
anti-SSB	anti-Sjögren's-syndrome-related antigen B
aPL	antiphospholipid antibodies
APS	antiphospholipid syndrome
ARA	American Rheumatism Association
AZA	azathioprine
BAFF	B-cell activating factor
BD	bis in die (twice a daily)
BICLA	British Isles Lupus Assessment Group-based Composite Lupus Assessment
BILAG	British Isles Lupus Activity Group
BLISS	Belimumab in Subjects with Systemic Lupus Erythematosus
BLyS	B-lymphocyte stimulator
BMD	bone mineral density
BMI	body-mass index
BSR	British Society for Rheumatology
C3	complement 3
C4	complement 4
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	cutaneous lupus erythematosus
CNI	calcineurin inhibitors
COX-2	cyclooxygenase-2
CPG	clinical practice guidelines
CrCl	creatinine clearance
CRP	C-reactive protein
CT	computed tomography
CYC	cyclophosphamide
CV	cardiovascular
CVD	cardiovascular disease
DG	development group
DMPA	depot medroxyprogesterone acetate
DOAC	direct oral anticoagulant
DORIS	Definition of Remission in SLE
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate

ELISA	enzyme-linked immunosorbent assay
EMG	electromyogram
ENA	extractable nuclear antigens
ESR	erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
EULAR/ACR	European Alliance of Associations for Rheumatology/American College of Rheumatology
EXPLORER	Exploratory Phase II/III SLE Evaluation of Rituximab
FBC	full blood count
FRAX	fracture risk assessment tool
g	gram
GI	gastrointestinal
GRADE	Grading Recommendations, Assessment, Development and Evaluation
h	hour
HCQ	hydroxychloroquine
hpf	high power field
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone replacement therapy
HTA	health technology assessment
HZ	Herpes Zoster
ICU	intensive care unit
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IIF	indirect immunofluorescence
IQR	interquartile range
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
kg	kilogram
LA	lupus anticoagulant
LDA	low dose aspirin
LFT	liver function test
LLDAS	lupus low disease activity state
LN	lupus nephritis
LUNAR	Lupus Nephritis Assessment with Rituximab
m^2	square metre
MaHTAS	Malaysian Health Technology Assessment Section
MD	mean difference
mg	milligram
min	minute
mL	millilitre
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTX	methotrexate
MOH	Ministry of Health
NIH	National Institutes of Health
NPSLE	neuropsychiatric SLE
NSAID	nonsteroidal anti-inflammatory drug
OD	once a day

OR	odds ratio
PE	plasma exchange
PO	per os (by oral)
PGA	Physician Global Assessment
QID	quarter in die (four times a day)
RBC	red blood cell
RNA	ribonucleic acid
RC	review committee
RCT	randomised controlled trial
RP	renal profile
RR	risk ratio
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SDI	SLICC/ACR Damage Index
SF-36	36-item Short Form Health Survey
SIR	standardised incidence ratio
SLAM-R	Systemic Lupus Activity Measure-Revised
SELENA-SLEDAI	Safety of Estrogens in Lupus Erythematosus: National Assessment - Systemic Lupus Erythematosus Disease Activity Index
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLEPDAI	Systemic Lupus Erythematosus Pregnancy Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SPF	sun protection factor
SRI	SLE Responder Index
TDM	therapeutic drug monitoring
TDS	ter die sumendum (three times a day)
TTP	thrombotic thrombocytopenic purpura
TULIP	Treatment of Uncontrolled Lupus via the Interferon Pathway
U.S.	United States
UFEME	urine full examination and microscopic examination
UPCR	urine protein/creatinine ratio
US	ultrasound
USPSTF	U.S. Preventive Services Task Force
VAS	Visual Analogue Scale
WBC	white blood cell
WHO	World Health Organization

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