

2020 Chinese guidelines for the diagnosis and treatment of systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease that represents a prodigious challenge of diagnosis and treatment. In 2019, under the leadership of the Chinese Rheumatology Association, a multidisciplinary guideline development group was established to develop an evidence-based diagnosis and treatment guideline for patients with SLE in PR China. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of evidence and the strength of recommendations. The guideline was reported following the Reporting Items for Practice Guidelines in Healthcare (RIGHT) checklist. In this guideline, we provided recommendations for SLE classification criteria, disease activity monitoring and assessment, medication administration and considerations for SLE patients with organs and systems involved, and management of special populations such as SLE patients in the setting of pregnancy. This guideline serves as an evidence-based tool for Chinese clinicians to diagnose and treat patients with SLE.

Keywords

lupus erythematosus • systemic • guideline • GRADE

Background

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, which is characterized by systemic multiple-organ involvement, relapses with large amount of autoantibodies. If patients with SLE do not receive prompt

treatment, they would get irreversible organ damage, which will ultimately lead to death. The causes of SLE are complicated, including genetics, sex hormones, exposure to various kinds of pathogens (e.g., viral and bacterial).^[1–3] The prevalence of SLE varies widely in different regions with a rate of 0–241/100,000. This number in mainland China is about 30–70/100,000,^[4, 5] and the ratio of male to female

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is 1:10–12.^[6–8] The survival rate of patients with SLE has increased due to the improvements in diagnosis and treatment. The 5-year survival rate of patients with SLE had increased from 50% to 60% in 1950s to more than 90% in 1990s and stabilized at 95% in high-income countries, at 92% in low-income and middle-income countries from 2008 to 2016.^[9–11] SLE is no longer an acute and highly lethal disease, but a chronic and controllable disease. Clinicians and patients play important roles in the awareness and attention of the disease and in emerging and optimizing scientific diagnosis and treatment of the disease.

Well known societies such as the European League Against Rheumatism (EULAR), the British Society of Rheumatology (BSR), and the Pan American League Against Rheumatism (PANLAR) have developed their own guidelines for the diagnosis and treatment of SLE.^[11–14] The Chinese Rheumatology Association also published the *Guidelines for the Diagnosis and Treatment of Systemic Lupus Erythematosus* in China in 2010.^[15] These guidelines have played an important role in promoting evidence-based clinical decision-making. However, there were still problems applying these guidelines to the Chinese SLE patients: (1) the Chinese Systemic Lupus Erythematosus Treatment and Research Group (CSTAR) registry cohort studies^[6, 16, 17] have shown that the incidence, clinical manifestations, and main clinical outcomes of patients with SLE in China are not completely identical to Europe and the United States; (2) the international guidelines for diagnosis and treatment of SLE did not include studies conducted in China, and thus did not appropriate for the clinical practice in China; (3) 10 years have passed since the publication of the Guideline for the Diagnosis and Treatment of Systemic Lupus Erythematosus by the Chinese Rheumatology Association. An update is now necessary. During this period, new diagnostic and therapeutic research results and new therapeutic medications have been emerging continuously. The concept, methods, and techniques for the diagnosis of SLE are constantly developing and updating, which make the previous Chinese guidelines inappropriate for the current SLE diagnosis and treatment in China. In view of this, with the methods and procedure in accordance with evidence-based clinical practice guidelines, based on the newest research evidences and Chinese clinical practice, Chinese Rheumatology Association, National Clinical Research Center for Dermatologic and Immunologic Diseases, and CSTAR worked together to establish “2020 *Chinese Guidelines for Diagnosis and Treatment of Systemic Lupus Erythematosus*” (hereinafter referred to as this guideline).

Guideline Development Methods

1. Guideline Initiator: This guideline was jointly initiated by Chinese Rheumatology Association, National Clinical Research Center for Dermatologic and Immunologic Diseases, and CSTAR. This work was started on March 21, 2019 and finalized on January 21, 2020.
2. Guideline Working Group: A multidisciplinary working group was established, which included experts in rheumatology, nephrology, dermatology, obstetrics, radiology, and evidence-based medicine. Retrieval and evaluation of the evidence was performed by the Center for Evidence-based Medicine of Lanzhou University/Chinese GRADE Center. All members of the Working Group had no direct conflict of interest with this guideline and signed a non-conflict of interest form.
3. Guideline Registration and Writing: The guideline was registered at the International Practice Guidelines Registry Platform, <http://www.guidelines-registry.org> (Registration number IPGRP-2019CN022). The content of this Guideline was designed and developed in accordance with the *World Health Organization Guideline Development Manual* issued by the World Health Organization in 2014,^[18] the *Basic Methods and Procedures for the Development/Revision of Clinical Diagnosis and Treatment Guidelines*, issued by the Chinese Medical Association in 2016.^[19] This guideline also refers to the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument^[20] and Reporting Items for Practice Guidelines in Healthcare (RIGHT).^[21, 22]
4. Guideline user and target population: This guideline is intended to advise rheumatologists, dermatologists, nephrologists, obstetricians, clinical pharmacists, imaging physicians, and professionals related to diagnose, treat, and manage patients with SLE. The recommendations of this guideline are for patients with SLE.
5. Selection and identification of clinical questions: By systematically reviewing the published guidelines and evaluation for SLE, and affiliating with interviews with some rheumatologists, the Working Group preliminary drafted 30 clinical questions and scenarios, followed by investigating and scoring the importance of clinical questions with online questionnaires. After 2 rounds of 83 surveys, 12 clinical questions in this guideline were finally selected.
6. Retrieval of evidence: The Evidence Evaluation Group deconstructed the clinical questions and outcome indicators of the final inclusion criteria according to the principle of Population, Intervention, Comparison, and Outcome (PICO). Based on the results of above deconstruction, the Evidence Evaluation Group retrieved: (1) systematic reviews, meta-analyses and network meta-analyses from MEDLINE, Cochrane Library, Epistemonikos, Chinese Biomedical Literature, Wanfang Database and China National Knowledge Infrastructure Database. The retrieved data was from the establishment of the database to September 2019; (2) UpToDate, DynaMed, MEDLINE, Chinese Biomedical Literature Database, Wanfang Database and China National Knowledge Infrastructure Database, mainly included original studies such as randomized controlled trials, cohort studies, case-control

- studies, case series studies and epidemiological surveys, and so on. The retrieved data was from the establishment of the database to September 2019; (3) Official websites, such as the National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), the American College of Rheumatology (ACR), EULAR, and the Asia-Pacific Alliance Against Rheumatism (APLAR), as well as the MEDLINE and China National Knowledge Infrastructure Databases, the retrieved data mainly included SLE related guidelines; (4) Supplement retrieval of Google Academia and other websites.
7. Evidence evaluation and grading: A Measurement Tool to Assess systematic Reviews (AMSTAR)^[23] was used by the Evidence Evaluation Group to evaluate the risk of bias of the included system evaluation, meta-analysis, and network meta-analysis. The methodological quality of the corresponding type of original studies was evaluated using the Cochrane Risk of Bias Assessment^[24] (ROB, for randomized controlled trial Studies), Quality Assessment Tool for Diagnostic Accuracy Studies^[25] (QUADAS-2, Diagnostic Accuracy Test Study), Newcastle-Ottawa Scale^[26] (NOS, for observational studies) and so on; the evaluation process was performed by two people independently, and if there was any disagreement, a third party was consulted to resolve the dispute. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was used to grade evidence and recommendations,^[27–31] as shown in Table 1.
 8. The formation of recommendations: Based on the summary of domestic and foreign evidence provided by the Evidence Evaluation Group, taking into consideration of preferences and values of patients in China, cost and advantages/disadvantages of interventions, the Working Group proposed recommendations that are consistent with the clinical diagnosis and treatment in China. Two rounds of Delphi recommendation surveys were conducted on October 05, 2019 and November 08, 2019. In total, 98 pieces of feedback were collected. Face to face discussion and modification from November 2019 to January 2020 were conducted to reach a consensus.
 9. Future updates of this *Guideline*: The recommendations of this guideline are planned to be updated within 3–5 years in accordance with the methodologies in International Guidelines.^[32]
- The summary of the recommendations is listed in Table 2.
- Recommendation 1: 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for systemic lupus erythematosus or 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus to make the diagnosis of SLE in patients with suspected disease (1B). In institutions that do not have a rheumatology or immunology department, we recommend consultation with a rheumatologist or immunologist via referral/tele-consultation (2C) for patients with atypical clinical manifestations or patients who are difficult to diagnose.**
- In order to improve the sensitivity and specificity of the classification for SLE, a set of classification criteria for SLE were jointly developed by EULAR and ACR in 2019 based on the classification criteria for SLE developed in 1997. This classification criteria includes 1 criterion for inclusion, 10 aspects, and 18 criteria. Infection, malignant tumor, medications, and other causes must be excluded before applying each criterion. Patients who met a certain criterion in the history should also be scored and take the highest weight score of each aspect into the total scores. A total score ≥ 10 can be classified as SLE.^[33] Validation cohort studies showed that the sensitivity of the SLE classification criteria of 2019 EULAR/ACR, 2012 SLICC, and 1997 ACR were 96%, 97%, and 83%, respectively, and the specificity was 93%, 84%, and 93%, respectively. Sensitivity and specificity of the 2019 EULAR/ACR classification criteria for SLE were appropriate; diagnostic accuracy studies for the new criteria showed that in adult SLE patients, the sensitivity of the SLE classification criteria of 2019 EULAR/ACR (initial draft), 2012 SLICC, and 1997 ACR were 93%, 100%, and 83%, respectively, and the specificity was 73%, 75%, and 82%, respectively. The 2012 SLICC classification criteria are shown to be appropriate in adult patients with SLE.^[33,34] Based on the results of the above studies, we recommend the use of these two

Table 1: Grading of the quality of evidence and strength of recommendations

Item	Contents
Grading of evidence Quality	
High (A)	Very confident: the observed value is close to the true value
Medium (B)	Moderate assurance of observed values: observations may be close to true values but may vary considerably
Low (C)	Limited assurance of the observed value: the observed value may differ greatly from the true value
Very low (D)	Almost unsure of the observed value: the observed value may differ extremely from the true value
Grading of recommendation strength	
Strong (1)	Clearly demonstrated that the intervention advantages outweigh the disadvantages or vice versa
Weak (2)	Uncertainty in advantages and disadvantages or evidence of comparable advantages and disadvantages regardless of quality

Table 2: Recommendation for the diagnosis and treatment of systemic lupus erythematosus**Recommendation 1**

2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for systemic lupus erythematosus or 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus to make the diagnosis of SLE in patients with suspected disease (1B). In institutions that do not have a rheumatology or immunology department, we recommend consultation with a rheumatologist or immunologist via referral/tele-consultation (2C) for patients with atypical clinical manifestations or patients who are difficult to diagnose.

Recommendation 2

The principles of treatment of SLE is early intervention and individualized treatment to minimize disease progression, reduce organ damage, and improve prognosis (1C). The short-term goals of SLE treatment are to control disease activity and improve clinical symptoms (1C), achieve clinical remission or the lowest possible disease activity. The long-term goals are to prevent and reduce relapse, reduce adverse medication reactions, prevent and control organ damage caused by the disease, and to achieve long-term sustained remission of the disease, reduce mortality and improve quality of life (1C).

Recommendation 3

For newly diagnosed patients with SLE and during followed-up, we recommended to use the SLE disease activity index (SLEDAI-2000) score criteria in combination with the physician's global assessment of disease activity (2C) for disease activity assessment. According to the SLEDAI-2000 score criteria, disease activity can be classified as mild activity (SLEDAI-2000 ≤ 6), moderate activity (SLEDAI-2000 7–12), and severe activity (SLEDAI-2000 > 12) (2D). For patients with active SLE, we recommended to assess the disease activity (2C) at least every month, and every 3–6 months for patients with stable disease. If relapse occurs, patients should be treated as active disease (2D).

Recommendation 4

Glucocorticoid is the basic medication for the treatment of SLE (1A). Individualized glucocorticoids regimens should be developed depending on disease activity and the type and severity of organ involvement. The lowest dose (1B) required to control the disease should be used for every patient. Low-dose glucocorticoids (≤ 10 mg/day prednisone or equivalent) may be considered if inadequate response to hydroxychloroquine or nonsteroidal anti-inflammatory drugs in mild patients; for patients with moderately active SLE, glucocorticoids (0.5–1 mg/kg/day prednisone or equivalent) combined with immunosuppressants should be considered (2C). For patients with severe active SLE, glucocorticoids (≥ 1 mg/kg/day prednisone or equivalent) combined with immunosuppressants should be considered. The dosage of glucocorticoids should be tapered when the disease is stabilized (2C). For patients with lupus crises, pulse glucocorticoids therapy combined with immunosuppressants should be used (1B). Clinicians should pay close attention to disease activity and adjust the glucocorticoids dosage according to disease activity. Tapering of glucocorticoids or withdrawal of glucocorticoid may be considered for patients with long-term stable disease (1C).

Recommendation 5

Long-term hydroxychloroquine is recommended as the basic treatment for patients with SLE without contraindication (1A). For patients taking hydroxychloroquine, ocular risk assessment is recommended. For high-risk patients, an annual ophthalmologic examination is recommended. Low-risk patients are advised to undergo an ophthalmologic examination (2C) annually from the fifth year of medication.

Recommendation 6

Immunosuppressants (2B) are recommended for patients who do not respond well to glucocorticoids in combination with hydroxychloroquine or who are unable to taper the dose of glucocorticoids below the safe dose (2B). Immunosuppressants are recommended at the time of initial treatment for patients with organ involvement (2C).

Recommendation 7

Biologics may be considered in patients who are refractory, intolerant to glucocorticoids and/or immunosuppressive therapy or relapse (2B)

Recommendation 8

Recommendation 8.1: For patients with Type I lupus nephritis, we recommend to treat the patient based on extrarenal manifestations (2C). For patients with type II lupus nephritis, we recommend treatment with glucocorticoids and/or immunosuppressants (2C).

Recommendation 8.2: For patients with Type III, Type IV, and complicated Type V (Type V + Type III or Type V + Type IV) lupus nephritis, we recommend that patients should be treated with glucocorticoids combined with cyclophosphamide (1B) or mycophenolate mofetil (1B) for induction therapy and mycophenolate mofetil (1B) or azathioprine (1B) for maintenance therapy.

Recommendation 8.3: For patients with simple Type V lupus nephritis and renal proteinuria, we recommend patients to be treated with moderate-dose glucocorticoids in combination with mycophenolate mofetil (1B) or calcineurin inhibitors (2B) or azathioprine (2B). Angiotensin converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) is recommended to help to control blood pressure strictly (2C).

Recommendation 8.4: It is recommended that the diagnosis of neuropsychiatric lupus should be based on clinical manifestations, serological test results, cerebrospinal fluid tests, and neuroimaging examinations. Neuropsychiatric lupus should be carefully differentiated from the neurological presentations caused by antiphospholipid syndrome (2C).

Recommendation 8.5: For patients with severe neuropsychiatric lupus, glucocorticoid pulse therapy (2B) is recommended as the first-line therapy, and cyclophosphamide (2B) may be combined if the response is unsatisfactory.

Recommendation 8.6: For patients with thrombocytopenia or autoimmune hemolytic anemia, glucocorticoids (2D) or intravenous immunoglobulin (2D) should be used for the treatment; and immunosuppressive medications (2D) may be added for those patients who do not respond well. Rituximab (2C) may be considered for patients with life-threatening hematologic involvement.

Recommendation 9

Patients who present with severe or refractory SLE, plasma exchange or immunoadsorption (2C) can be considered. For patients who present with refractory SLE or infection, intravenous immunoglobulin (2D) may be considered in addition to the standard treatment.

Recommendation 10

Infection is the first cause of death in patients with SLE. The potential risk of infection must be assessed in a timely manner throughout the treatment of SLE (1B).

Recommendation 11

For women with SLE at childbearing age, pregnancy may be considered if the disease activity is stable for at least 6 months without vital organ damage, and the discontinuation of potentially teratogenic medications for a sufficiently safe period of time (2B). If pregnancy is planned, counseling with Rheumatology and Obstetrics specialists and general assessment must be conducted before the start of planning for pregnancy (1B). For pregnant patients, disease activity and fetal growth must be closely monitored (1C). If there is no contraindication, hydroxychloroquine (1B) is recommended throughout pregnancy. For patients who are currently pregnant and have active disease, glucocorticoid and azathioprine can be used to control the disease (2C).

Recommendation 12

Lifestyle modifications is an important component in the management of SLE. We recommend that patients with SLE should follow the following principles:

- (1) avoid exposure to some hazardous substances;
- (2) avoid sun exposure;
- (3) moderate exercise;
- (4) seeking for psychological support, if necessary;
- (5) quit smoking;
- (6) vitamin D supplement (1C).

classification criteria for patients with SLE in China. However, only the SLE classification criteria of 1997 ACR was validated in the Chinese population with SLE, the results showed that the criteria had good applicability for Chinese patients with SLE.^[35,36] Thus, in the future, it is necessary to validate the applicability of 2012 SLICC and 2019 EULAR/ACR classification criteria for Chinese SLE patients.

A cross-section study showed that only 23% of 71 patients with SLE diagnosed by primary health care physicians actually could meet the 1997 ACR classification criteria for SLE (meeting ≥ 4 criteria), whereas among the 249 patients with SLE diagnosed by rheumatologist, 79% of patients could meet the 1997 ACR classification criteria for SLE (meeting ≥ 4 criteria).^[37] Obviously, the participation of rheumatologists in the diagnosis of patients with SLE is helpful to improve the accuracy of diagnosis.

Recommendation 2: The principles of the treatment of SLE is early intervention and individualized treatment to minimize disease progression, reduce organ damage, and improve prognosis (1C). The short-term goals of SLE treatment are to control disease activity and improve clinical symptoms (1C), achieve clinical remission or the lowest possible disease activity. The long-term goals are to prevent and reduce relapse, reduce adverse medication reactions, prevent and control organ damage caused by the disease, and to achieve long-term sustained remission of the disease, reduce mortality and improve quality of life (1C).

Studies have shown that early high disease activity increases the risk of organ damage and death, and that early diagnosis and treatment are beneficial for controlling disease and improving patient outcomes.^[38] At present, the treatment of SLE includes glucocorticoids (hereinafter referred to as glucocorticoids), antimalarials, immunosuppressants, biologics, and other medications. Different kinds of drugs have great differences in efficacy and adverse reactions, individualized treatment strategy according to the specific situation of patients should be considered.^[12, 13, 15]

The definition of disease remission in SLE remains to be determined. The current consensus is that SLE should be controlled in the ideal state of clinical remission. If clinical remission could not be achieved, the disease activity should be controlled to the lowest possible disease activity.^[39] Approximately 25% of patients with ≤ 4 years duration of SLE achieved clinical remission with treatment, and 45% had organ damage. Relapse is common in patients with SLE, and the risk of relapse is 60% in 4 years of disease duration.^[40] Relapse is a marker of significantly increase of disease activity, also a major cause of organ damage and adverse prognosis. High-risk factors for relapse include younger age at disease onset, sustained clinical disease activity, and serological active disease. After achieving remission or minimal disease activity, treatment

strategies usually need to be adjusted to prevent and reduce relapse. As shown in a cohort study, compared with the patients with SLE whose disease activity could not be controlled effectively, patients who could achieve disease remission ($HR = 0.60$, 95% CI 0.43–0.85) and low disease activity ($HR = 0.66$, 95% CI 0.48–0.93) have reduced new damage and better prognosis.^[41] In general, the long-term goal of SLE treatment is to prevent and reduce relapse, decrease organ damage, reduce mortality, improve survival rate and quality of life.

Recommendation 3: For newly diagnosed patients with SLE and during follow-up, we recommend to use the SLE disease activity index (SLEDAI-2000) score criteria in combination with the physician's global assessment of disease activity (2C) for disease activity assessment. According to the SLEDAI-2000 score criteria, disease activity can be classified to mild activity (SLEDAI-2000 ≤ 6), moderate activity (SLEDAI-2000 7–12), and severe activity (SLEDAI-2000 > 12) (2D). For patients with active SLE, we recommend to assess the disease activity (2C) at least every month, and every 3–6 months for patients with stable disease. If relapse occurs, patients should be treated as active disease (2D).

There are 7 SLE disease activity assessment tools^[42–49] available. Each of the tools requires physician to comprehensively assess individual patient's disease history based on physical examination and laboratory test results. There are several factors that influence the choice of assessment tools: the physician's personal preferences and knowledge, assessment tools available (whether the tool needs to use a computer, cost of tests), the time needed to complete the assessment.^[50] Currently, SLEDAI-2000 and BILAG-2004 are commonly used to assess disease activity in clinical practice in PR China. The scores of SLEDAI-2000 were 0–105, and the results of BILAG-2004 were classified into 5 categories: A, B, C, D, and E. SLEDAI-2000 should be preferentially selected because of the shorter assessment time compared with BILAG-2004, and simplified Mexican version eliminated immunological testing, which made the assessment easier.^[51]

There are some criteria for grading disease activity based on SLEDAI-2000, and the main four disease activity grading criteria are discussed in this guideline.^[12, 13, 15, 52] We recommend to use the criteria proposed by EULAR, that is, SLEDAI-2000 ≤ 6 for mild activity, 7–12 for moderate activity, and SLEDAI-2000 > 12 for severe activity.^[12] Since high SLEDAI-2000 score predicted increased risk of organ damage ($HR = 1.18$, 95% CI 1.02–1.37) and increased risk of death ($HR = 1.14$, 95% CI 1.02–1.22),^[38] regular monitoring of disease activity and organ damage in patients with SLE is required. Due to limitations of the assessment of disease activity based on SLEDAI-2000 and BILAG-2004, the physician global assessment (PGA) is also required. Involving clinical and other manifestations of SLE, PGA could improve the accuracy of the assessment.

Currently, no evidence indicates the frequency of clinical monitoring in patients with SLE. The UK SLE Guidelines recommend that disease activity should be assessed at least every 1–3 months for patients with active disease, whereas the Spanish SLE Guidelines recommend that disease activity should be assessed at least every 3–4 months for 1 year. For patients with SLE in a stable disease or with low disease activity, both the UK and Spanish SLE Guidelines recommended that they should be assessed every 6–12 months.^[13,53] We recommend that disease activity should be assessed at least once per month in patients with active SLE (consensus: 83.33%) and every 3–6 months for patients with a stable disease (consensus: 94.44%). The SDI (SLICC damage index) is the only internationally recognized and validated assessment tool for organ damage in SLE. This tool scores 12 organ systems independently, is an effective tool for evaluating organ damage in clinical practice and provides a basis for better judging the prognosis of patients with SLE.^[54] In addition, the frequency of clinical monitoring should be adjusted according to the progression of the disease and intensity of treatment. If relapse, the disease must be treated as an active disease, and the disease activity must be assessed at least once every month until the disease becomes stable.

We recommend using Chinese Rheumatism Data Center (CRDC) chronic disease management platform for follow-up of patients with SLE^[55] in China.

Recommendation 4: Glucocorticoid is the basic medication for the treatment of SLE (1A). Individualized glucocorticoids regimens should be developed depending on disease activity and the type and severity of organ involvement. The lowest dose (1B) required to control the disease should be used for every patient. Low-dose glucocorticoids (≤ 10 mg/day prednisone or equivalent) may be considered if inadequate response to hydroxychloroquine or nonsteroidal anti-inflammatory drugs in mild patients; for patients with moderately active SLE, glucocorticoids (0.5 to 1 mg/kg-d prednisone or equivalent) combined with immunosuppressants should be considered (2C). For patients with severe active SLE, glucocorticoids (≥ 1 mg/kg-d prednisone or equivalent) combined with immunosuppressants should be considered. The dosage of glucocorticoids should be tapered when the disease is stabilized (2C). For patients with lupus crises, pulse glucocorticoids therapy combined with immunosuppressants should be used (1B). Clinicians should pay close attention to disease activity and adjust the glucocorticoids dosage according to disease activity. Tapering of glucocorticoids or withdrawal of glucocorticoid may be considered for patients with long-term stable disease (1C).

Glucocorticoid plays a crucial role in the treatment of SLE and is the most commonly used medication for the

remission induction treatment of SLE, and also the basic medication for the control of disease activity. Glucocorticoid is recommended by international guidelines for the treatment of SLE.^[12, 13, 15, 53, 56, 57]

For patients with SLE, individualized glucocorticoids therapy should be established according to disease activity, type and severity of organ involvement. The dosage should be adjusted according to disease activity, duration of medication use, and adverse reactions.

Patients with mildly active SLE generally do not require glucocorticoids therapy. When hydroxychloroquine or nonsteroidal anti-inflammatory medications could not adequately control the disease, low-dose glucocorticoids (prednisone ≤ 10 mg/day or equivalent) may be considered to help control disease activity.^[12, 13, 15, 53, 56, 57]

For patients with moderate active SLE, moderate doses of prednisone (0.5 to 1 mg kg⁻¹ d⁻¹), or equivalent doses are recommended. In patients whose disease failed to under control by glucocorticoid alone, immunosuppressants may be used to reduce the cumulative dose of glucocorticoids and the risk of long-term adverse reactions.^[13, 15, 56]

For patients with severe active SLE, 1 mg kg⁻¹ d⁻¹ prednisone or equivalent in combination with immunosuppressants are recommended, with glucocorticoid dose adjustments after disease stabilization.^[15,56] In patients with severe SLE, pulse glucocorticoids therapy may be used if necessary.^[12,53,57]

Glucocorticoids pulse therapy combined with immunosuppressive agents are recommended for SLE patients with lupus crisis. Glucocorticoids pulse therapy is intravenous methylprednisolone 500–1,000 mg d⁻¹, usually over 3 consecutive days as a course of treatment. This regimen could be repeated in 5–30 days interval if necessary. After pulse therapy, prednisone 0.5–1 mg kg⁻¹ d⁻¹ or equivalent should be taken orally, usually for 4–8 weeks, but the duration of treatment depends on the patient's condition.^[15,56] Pulse therapy resulted in rapid disease control without significant increased adverse reactions compared with conventional doses of glucocorticoids therapy.^[58]

The time of glucocorticoid tapering and discontinuation depends on disease activity and the side effects. Abrupt discontinuation of glucocorticoid should be avoided. For patients with stable disease, the dose tapering must be started as soon as possible, and must be gradual and slow to avoid disease relapse.^[59]

More than 30% of patients who take glucocorticoids may have adverse reactions. The most common recent adverse reactions are GI discomfort, agitation, palpitations and insomnia. Long-term adverse reactions include secondary infection,

Table 3: Equivalent dose of commonly used glucocorticoids

Drug category	Drug name	Equivalent dose (mg)
Short-term effects	Hydrocortisone	20
	Cortisone	25
	Prednisone	5
Intermediate-term effects	Prednisolone	5
	Methylprednisolone	4
Long-term effects	Triamcinolone acetonide	4
	Betamethasone	0.60
	Dexamethasone	0.75

osteoporotic fracture and so on.^[60] Because adverse effects of glucocorticoids are dose dependent, clinicians should use the lowest dose needed for disease control and should also avoid the risk of underuse or misuse. Previous studies have shown that patients with SLE receiving prednisone > 7.5 mg d⁻¹ are more likely to develop glucocorticoids-related cardiovascular disease (including myocardial infarction, heart failure and cerebrovascular disease), kidney disease, musculoskeletal disease. But treatment with ≤ 7.5 mg d⁻¹ prednisone was not associated with cumulative impairment in patients with SLE.^[61, 62] Tapering and discontinuation of glucocorticoids may be considered in patients with long-term stable disease. Equivalent doses of commonly used glucocorticoids are shown in Table 3.^[63]

Recommendation 5: Long-term hydroxychloroquine is recommended as the basic treatment for patients with SLE without contraindication (1A). For patients taking hydroxychloroquine, ocular risk assessment is recommended. For high-risk patients, an annual ophthalmologic examination is recommended. Low-risk patients are advised to undergo an ophthalmologic examination (2C) annually from the fifth year of medication.

Long-term use of hydroxychloroquine in patients with SLE reduces disease activity, the risk of organ damage, thrombosis, and improves lipid profile and survival rate.^[64–67] Hydroxychloroquine-induced retinopathy is observed 5 years after hydroxychloroquine administration. High-risk populations (long-term use and/or use of high-dose hydroxychloroquine, concomitant hepatic and renal disease, concomitant use of tamoxifen, history of retinal or macular disease and advanced age) should have ophthalmologic examinations before and after treatment annually.^[68–70] Patients taking hydroxychloroquine without high-risk factors should undergo basic and annual ophthalmologic examinations 5 years later after taking the medicine to monitor drug-induced retinopathy.^[71, 72]

Recommendation 6: Immunosuppressants (2B) are recommended for patients who do not respond well to

glucocorticoids in combination with hydroxychloroquine or who are unable to taper the dose of glucocorticoids below the safe dose (2B). Immunosuppressants are recommended at the time of initial treatment for patient with organ involvement (2C).

The use of immunosuppressants reduces the cumulative dose of glucocorticoids and prevents disease relapse.^[31] In patients with refractory (poor response to conventional therapy) or relapsed SLE, immunosuppressants can reduce glucocorticoids dosage, control disease activity and improve clinical remission rates.^[73, 74]

Initial treatment of lupus nephritis (induction remission), the combination of immunosuppressants significantly increases the clinical remission rate and reduces the rate of treatment failure compared with glucocorticoids monotherapy; therefore, the addition of immunosuppressants^[75, 76] in patients with SLE with organ involvement should be considered at the time of initial treatment, and should choose appropriate immunosuppressants according to clinical manifestations, fertility requirements, drug safety and cost (Table 4).^[77–96]

Recommendation 7: Biologics may be considered in patients who are refractory, intolerant to glucocorticoids and/or immunosuppressive therapy (2B) or relapsed.

For patients with refractory (poor response to conventional treatment) or relapsed SLE, the use of biologics significantly increases the complete and partial remission rates and reduces disease activity, relapse rate and glucocorticoids dosage.^[98–101] Although many biological agents have been tried in the treatment of SLE and have achieved certain clinical efficacies, only Belimumab was approved by the United States Food and Drug Administration (FDA) and the China Food and Drug Administration (CFDA) for the treatment of SLE currently. However, the efficacy and safety of Belimumab in the treatment of Chinese patients with SLE need to be further validated. The advantages and common adverse reactions of different types of biologics are shown in Table 5.

Recommendation 8.1: For patients with Type I lupus nephritis, we recommend to treat the patient based on extrarenal manifestations (2C). For patients with Type II lupus nephritis, we recommend treatment with glucocorticoids and/or immunosuppressants (2C).

Recommendation 8.2: For patients with Type III, Type IV and complicated Type V (Type V + Type III or Type V + Type IV) lupus nephritis, we recommend that patients should be treated with glucocorticoids combined with cyclophosphamide (1B) or mycophenolate mofetil (1B) for induction therapy and mycophenolate mofetil (1B) or azathioprine (1B) for maintenance therapy.

Table 4: Indications, advantages and common and significant adverse reactions of different immunosuppressants

Immunosuppressants	Main applicable populations	Advantages	Common adverse reactions
Mycophenolate mofetil	Patients with moderate to severe SLE ^[74]	In patients with moderate to severe lupus nephritis, mycophenolate mofetil is an effective treatment in the induction and maintenance phases, and in reducing the relapse rate. ^[77]	The most common adverse reactions are gastrointestinal discomfort. Some patients develop infections, myelosuppression and liver damage, ^[78] and due to teratogenicity, pregnancy can only be attempted at least 6 weeks after discontinuation. ^[79]
Cyclophosphamide	Moderate to severe lupus nephritis, neuropsychiatric lupus and SLE with immune thrombocytopenia ^[75, 80, 97]	For induction and maintenance treatment. It is effective in patients with moderate to severe lupus nephritis, and is an effective immunosuppressive agent for the treatment of neuropsychiatric and hematological disease. ^[75, 80]	Common adverse reactions are gastrointestinal discomfort, nausea, vomiting. Liver damage and myelosuppression are the main adverse reactions. Long-term high-dose use will increase the risk of tumors. Since it has gonadotoxicity and teratogenicity, it is recommended to discontinue at least 3 months before pregnancy ^[81, 82, 97]
Leflunomide	Proliferative lupus nephritis ^[83, 84]	It is effective and well tolerated in some proliferative lupus nephritis patients ^[84]	Leflunomide causes liver damage, hypertension, leukopenia, infection and some other complications. Because of teratogenicity, it is recommended that pregnancy should only be attempted for 6 months after drug withdrawal. ^[85, 86]
Methotrexate	Patients with mild to moderate SLE without renal involvement ^[97]	It has good efficacy in improving skin, arthritis and overall condition in patients with SLE. ^[87, 97]	The most common adverse reactions are gastrointestinal discomfort, such as nausea, vomiting. Hematological adverse reactions such as anemia, leukopenia and liver damage are common. Discontinuation of this medication 1–3 months before pregnancy is recommended given its teratogenicity. ^[86–88]
Tacrolimus	Proliferative lupus nephritis, refractory lupus nephritis and SLE with immune thrombocytopenia ^[77, 89–91]	It is effective in the induction and maintenance treatment of lupus nephritis. It can also reduce relapse. ^[77] It can be used for the treatment of refractory lupus nephritis, especially in those with proteinuria. ^[89, 90] Compared with other immunosuppressants or glucocorticoids, it has low risk of causing serious infections. ^[92]	Common adverse reactions are gastrointestinal discomfort, renal and liver function impairment. The dosage of tacrolimus must be reduced in patients with impaired hepatic function and renal dysfunction. Blood glucose and blood pressure should be monitored during administration. ^[93]
Cyclosporine	Lupus nephritis and SLE with immune thrombocytopenia ^[94–96]	Cyclosporine in combination with other immunosuppressants may be used to treat lupus nephritis that does not respond to standard therapy, it is effective in some patients with hematological involvement. ^[94, 95]	The main adverse reactions are renal impairment, elevation of blood pressure and increased risk of infection. ^[95]
Azathioprine	Patients with moderate SLE ^[79]	Maintenance treatment for SLE. It has low risk for severe infection. It is safe during pregnancy. ^[79]	The main adverse reactions are myelosuppression and liver damage. ^[79] Testing for thiopurine methyltransferase activity is required.

SLE, Systemic lupus erythematosus.

Table 5: The advantages and significant adverse reactions of biologics in the treatment of systemic lupus erythematosus

Biologics	Approved by FDA and CFDA	Advantages	Significant adverse reactions
Belimumab	Yes	It can improve the patients' serological indexes, reduce the risk of severe relapse and the dosage of glucocorticoids. It could be considered for patients who are poorly controlled with current conventional therapy.	Common adverse reactions are infections, headache, and nausea
Rituximab	No	For patients with refractory lupus nephritis and hematologic involvement, the disease can be controlled, and the dosage of glucocorticoids can be reduced. ^[98, 101]	Common adverse reactions include infections and infusion reactions. ^[98]

FDA, Food and Drug Administration; CFDA, China Food and Drug Administration.

Recommendation 8.3: For patients with simple Type V lupus nephritis and renal proteinuria, we recommend patients to be treated with medium-dose glucocorticoids in combination with mycophenolate mofetil (1B) or calcineurin inhibitors (2B) or azathioprine (2B). Angiotensin converting enzyme inhibitor (ACEI)/angiotensin II

receptor blocker (ARB) is recommended to help control blood pressure strictly (2C).

Recommendation 8.4: It is recommended that the diagnosis of neuropsychiatric lupus should be based on clinical manifestations, serological test results, cerebrospinal fluid

tests and neuroimaging examinations. Neuropsychiatric lupus should be carefully differentiated from the neurological presentations caused by antiphospholipid syndrome (2C).

Recommendation 8.5: For patients with severe neuropsychiatric lupus, glucocorticoid pulse therapy (2B) is recommended as first-line therapy, and cyclophosphamide (2B) may be combined if the response is unsatisfactory.

Recommendation 8.6: For patients with thrombocytopenia or autoimmune hemolytic anemia, glucocorticoids (2D) or intravenous immunoglobulin (2D) should be used for the treatment; and immunosuppressive medications (2D) may be added to those patients who do not respond well. Rituximab (2C) may be considered for patients with life-threatening hematologic involvement.

Indications of renal biopsy and pathological classification of lupus nephritis should be conducted according to the latest guidelines and criteria to provide guidance for subsequent treatment.^[102–104] For patients with Type II lupus nephritis who are at risk of histological transformation,^[105, 106] particularly for patients who do not respond well to initial therapy, treatment with glucocorticoids and/or immunosuppressants are recommended. One network meta-analysis showed that mycophenolate mofetil was comparable to intravenous cyclophosphamide in patients with Type III/IV/V + III/V + IV lupus nephritis undergoing induction therapy. The complete remission rate was similar to intravenous cyclophosphamide ($OR = 1.44$, 95% CI 1.00–2.06), and that of calcineurin inhibitors ($OR = 1.74$, 95% CI 1.09–2.79). Mycophenolate mofetil was associated with a lower risk of relapse compared with azathioprine in patients with Type III/IV/V + III/V + IV lupus nephritis undergoing maintenance therapy ($OR = 0.53$, 95% CI 0.31–0.90). There was no significant difference in the risk of relapse between calcineurin inhibitors ($OR = 0.64$, 95% CI 0.22–1.88) and cyclophosphamide ($OR = 1.68$, 95% CI 0.51–5.51).^[75] However, another meta-analysis showed that there were no statistically significant differences in mortality, incidence of end-stage renal disease, nor disease relapse between mycophenolate mofetil and azathioprine during the maintenance treatment period.^[107]

One network meta-analysis showed that glucocorticoids in combination with mycophenolate mofetil and calcineurin inhibitors were more effective than glucocorticoids monotherapy in inducing remission of Type V lupus nephritis (most with renal proteinuria). The effect of azathioprine combined with glucocorticoids was not significantly different from glucocorticoids monotherapy.^[76] Patients with simple Type V lupus nephritis without renal proteinuria have a good prognosis and only require ACEI/ARB for blood pressure control without immunosuppressive therapy.^[108]

At present, there are no well-accepted diagnostic criteria and specific laboratory indicators for neuropsychiatric lupus, so the diagnosis of neuropsychiatric lupus is basically exclusive. For patients with diffused neuropsychiatric lupus, CSF antibodies and anti-ribosomal P antibodies are helpful. For patients with focal neuropsychiatric lupus, antiphospholipid antibodies or abnormal brain magnetic resonance imaging (MRI) findings are helpful for diagnosis.^[109] MRI abnormalities (including brain atrophy, T_1 - and T_2 -weighted lesions, etc.) are more common in patients with neuropsychiatric lupus and related to specific manifestations of neuropsychiatric lupus, so MRI is an effective imaging examination for the diagnosis of neuropsychiatric lupus.^[110]

For severe neuropsychiatric lupus patients, high-dose methylprednisolone pulse therapy combined with intravenous cyclophosphamide can improve their psychiatric symptoms, and the efficacy is superior to methylprednisolone pulse therapy alone, with a total improvement rates of 94.7% and 46.2%, respectively.

The initial remission rate of glucocorticoids therapy in SLE with severe autoimmune hemolytic anemia can reach 96%, the effectiveness rate of treatment of SLE related immune thrombocytopenia can reach 80%. Treatment with intravenous immunoglobulins and glucocorticoids in combination with immunosuppressants can improve hematologic symptoms in SLE patients with autoimmune hemolytic anemia.^[111–113] For SLE patients with severe refractory thrombocytopenia, treatment with low-dose rituximab (100 mg intravenously weekly for 4 times) has an 80% response rate, which improved patient outcomes effectively. Rituximab is an effective treatment in patients with life-threatening acute hemolytic anemia.^[114–116]

Recommendation 9: Patients with severe or refractory SLE, plasma exchange or immunoadsorption (2C) can be considered. For patients who present with refractory SLE or infection, intravenous immunoglobulin (2D) may be considered in addition to the standard treatment.

In 2018, an epidemiological survey of blood purification treatment of severe pediatric SLE was conducted in 22 hospitals by the Blood Purification Committee of the Pediatrician Association, Chinese Medical Doctor Association. The survey results showed that plasma exchange and DNA immunoadsorption could improve the clinical symptoms of severe pediatric SLE patients, with the improvement rates of 87.3% and 87.8%, respectively.^[117] Plasma exchange and immunoadsorption can improve clinical symptoms in the short term in severe or refractory SLE patients, but cannot improve their final outcomes. Therefore, Plasma exchange and immunoadsorption can be used as adjunct treatments.^[118, 119]

Intravenous immunoglobulins may improve clinical outcomes in patients with refractory SLE or infection, but the quality of evidence is very low.^[120, 121]

Tripterygium wilfordii is an effective treatment of SLE. However, more attention must be paid to its reproductive toxicity. The reported incidence rate of reproductive toxicity is 17.9% (95% CI 0.14–0.22).^[122, 123]

Recommendation 10: Infection is the leading cause of death in patients with SLE. The potential risk of infection must be assessed in a timely manner throughout the treatment of SLE (1B).

The proportion of patients with SLE dying from infection is increasing year by year in China, and infection has become the leading cause of death in patients with SLE in China. The mortality of infection is exceeding 50%^[124] in SLE patients. Inappropriate use of glucocorticoids ($OR = 3.05$, 95% CI 1.15–8.07) and immunosuppressants ($OR = 2.01$, 95% CI 1.21–3.32), high SLEDAI ($OR = 0.44$, 95% CI 0.32–0.59), multiple organs involvement ($OR = 2.53$, 95% CI 1.87–3.42), and younger age at disease onset ($OR = 2.09$, 95% CI 1.50–2.91) are major risk factors for infection in SLE patients.^[92, 125] Serum high-sensitive C-reactive protein above 50 mg/L, procalcitonin above 0.5 µg/L and lymphocyte count $\leq 1.0 \times 10^9/L$ suggests an increased risk of infection ($HR = 4.7$, 95% CI 1.6–13.7).^[126–128] The clinical manifestations of patients should be assessed timely to identify potential infection.

Recommendation 11: For women with SLE at childbearing age, pregnancy may be considered if the disease activity is stable for at least 6 months without vital organ damage, and the discontinuation of potentially teratogenic medications for a sufficiently safe period of time (2B). If pregnancy is planned, counseling with Rheumatology and Obstetrics specialists and general assessment must be conducted before the start of planning for pregnancy (1B). For pregnant patients, disease activity and fetal growth must be closely monitored (1C). If there is no contraindication, hydroxychloroquine (1B) is recommended throughout pregnancy. If patients who are currently pregnant and have active disease, glucocorticoid and azathioprine can be used to control the disease (2C).

In order to reduce the complications of pregnancy and improve maternal and fetal outcomes in women with SLE, adequate preparation must be made before conception, and disease activity must be closely monitored during pregnancy. Women with significant impaired organ function and/or with severe organ damage should be informed of pregnancy-related risks.^[129, 130] Compared with patients with inactive lupus nephritis, patients with active lupus nephritis have significantly increased risk for poor maternal outcomes ($OR = 2.04$, 95% CI 1.21–3.45),

pre-eclampsia or eclampsia ($OR = 2.62$, 95% CI 1.36–5.05), fetal loss ($OR = 4.90$, 95% CI 1.54–15.59), preterm delivery ($OR = 4.26$, 95% CI 2.19–8.31).^[131] Patients with persistent remission for more than 6 months, proteinuria < 0.5 g/d, no renal failure, and cytotoxic drug withdrawal for > 1 year before pregnancy, have better pregnancy outcome including full term delivery rate (76.47% vs. 23.08%), live birth rate (80.39% vs. 30.77%), the risk of pregnancy-induced hypertension (17.65% vs. 23.08%), and preeclampsia or eclampsia (9.80% vs. 15.38%) when compared with patients with active disease in the preceding 6 months of pregnancy.^[132]

Preconception counselling is essential for successful pregnancy, and planned pregnancy can significantly reduce the risk of disease relapse and adverse maternal and fetal outcomes during pregnancy compared with accidental pregnancy.^[133, 134] Active disease itself could significantly increase the risk of adverse pregnancy outcomes.^[135] so the disease must be strictly controlled before pregnancy. A multidisciplinary team (including rheumatologists and obstetricians at least) must assess patients before pregnancy and decide whether the patient is suitable for pregnancy. Patient's disease activity must be strictly monitored throughout pregnancy in order to achieve the goal of improving maternal and fetal outcomes.^[136, 137] Multidisciplinary management of pregnant patients with SLE by rheumatologists and obstetricians can be referred to the *Recommendations for Perinatal Management of Chinese Patients with Systemic Lupus Erythematosus*.^[138]

Strict surveillance of disease activity and fetal growth during pregnancy are essential for better maternal and fetal outcomes. Risk factors associated with complications during pregnancy, such as antiphospholipid syndrome, must be screened and tested before pregnancy. Patients must be strictly monitored during pregnancy for disease activity, placental function and fetal growth.^[137–141]

Hydroxychloroquine may reduce the rate of preterm birth, disease relapse, disease activity and risk of adverse fetal outcomes in pregnant women with SLE. Continuous hydroxychloroquine therapy may reduce disease relapse during pregnancy and postpartum. If there is no contraindication, we recommend continuing HCQ treatment throughout pregnancy. For active SLE patients during pregnancy, glucocorticoid and hydroxychloroquine in addition to immunosuppressants available during pregnancy may be considered for disease control.^[142–144] The use of azathioprine during pregnancy does not cause fetal teratogenesis and may reduce the risk of disease relapse and improve fetal outcome.^[145] Hydroxychloroquine, glucocorticoid, azathioprine, cyclosporine A and tacrolimus may be used to prevent or control SLE relapse during pregnancy, but mycophenolate mofetil, cyclophosphamide, leflunomide and methotrexate should be avoided.^[86]

Recommendation 12: Lifestyle modifications is an important component in the management of SLE. We recommend that patients with SLE should follow the following principles: (1) avoid exposure to some hazardous substances; (2) avoid sun exposure; (3) moderate exercise; (4) seeking for psychological support if necessary; (5) quit smoking; (6) vitamin D supplement (1C).

Skin is one of the most frequently involved organs in SLE and is one of the main organ systems that perceive changes in the external environment. Some cosmetics may contain substances that may induce lupus erythematosus or aggravate the disease.^[146, 147] In addition, patients with SLE should avoid exposure to hair dyes, eyebrow tattoos etc.^[148, 149] Ultraviolet radiation can induce SLE and sun protection (e.g., sun cream) can protect patients from UV-induced skin irritation, reduce skin inflammation^[150–152] and disease relapse. Patients receiving exercise intervention can reduce depression (SMD = -0.40 , 95% CI -0.71 to -0.09) and fatigue (MD = -0.52 , 95% CI -0.91 to -0.13).^[153, 154] Psychological intervention can reduce anxiety (SMD = -0.95 , 95% CI -1.57 to -0.34), mental stress (SMD = -0.63 , 95% CI -1.02 to -0.23) and depression (SMD = -1.14 , 95% CI -1.84 to -0.44), which is helpful for disease activity control (SMD = -0.34 , 95% CI -0.57 to -0.11).^[151] Patients who smoke have an increased risk of morbidity (OR = 1.49 , 95% CI 1.06 to 2.08) and a higher SLEDAI (15.6 ± 7.8 vs. 9.0 ± 5.8) than patients who do not smoke.^[155, 156] Osteoporosis is a major co-morbidity in patients with SLE. Serum vitamin D level is significantly lower in patients with SLE than in healthy subjects, and vitamin D supplementation reduces the inflammation and disease activity in patients with SLE.^[157, 158]

A diagram of the diagnosis and treatment pathway for systemic lupus erythematosus (SLE) is shown in Figure 1.

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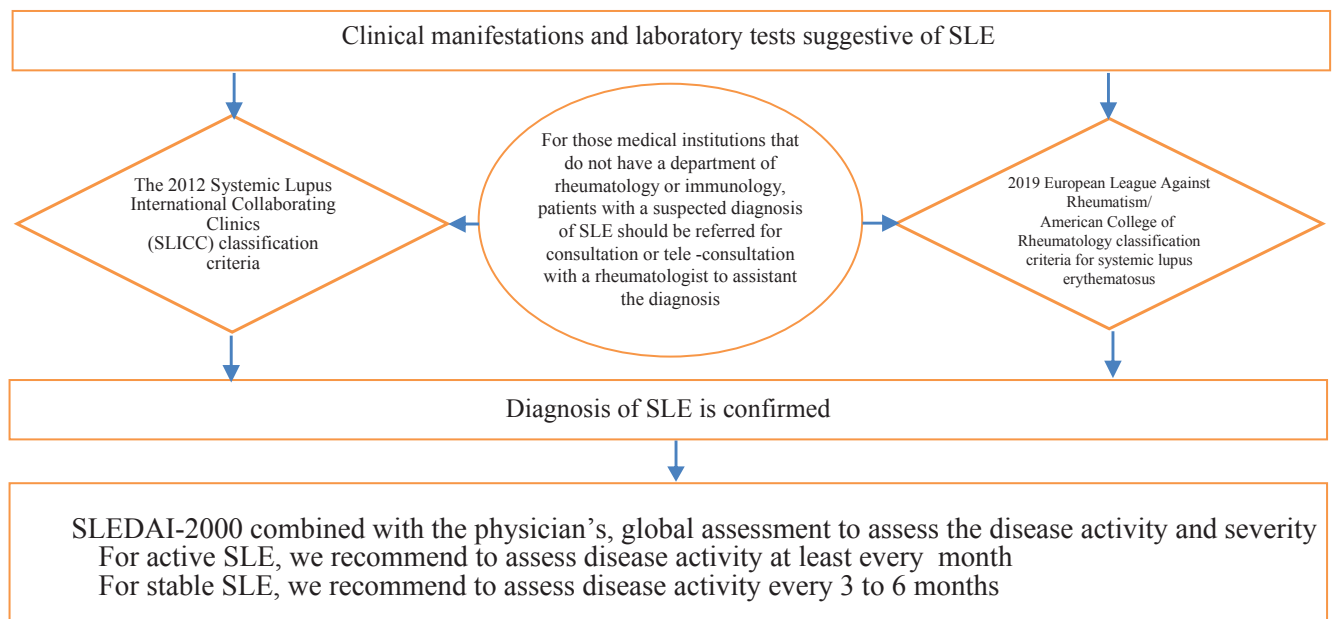


Figure 1: (Continued).

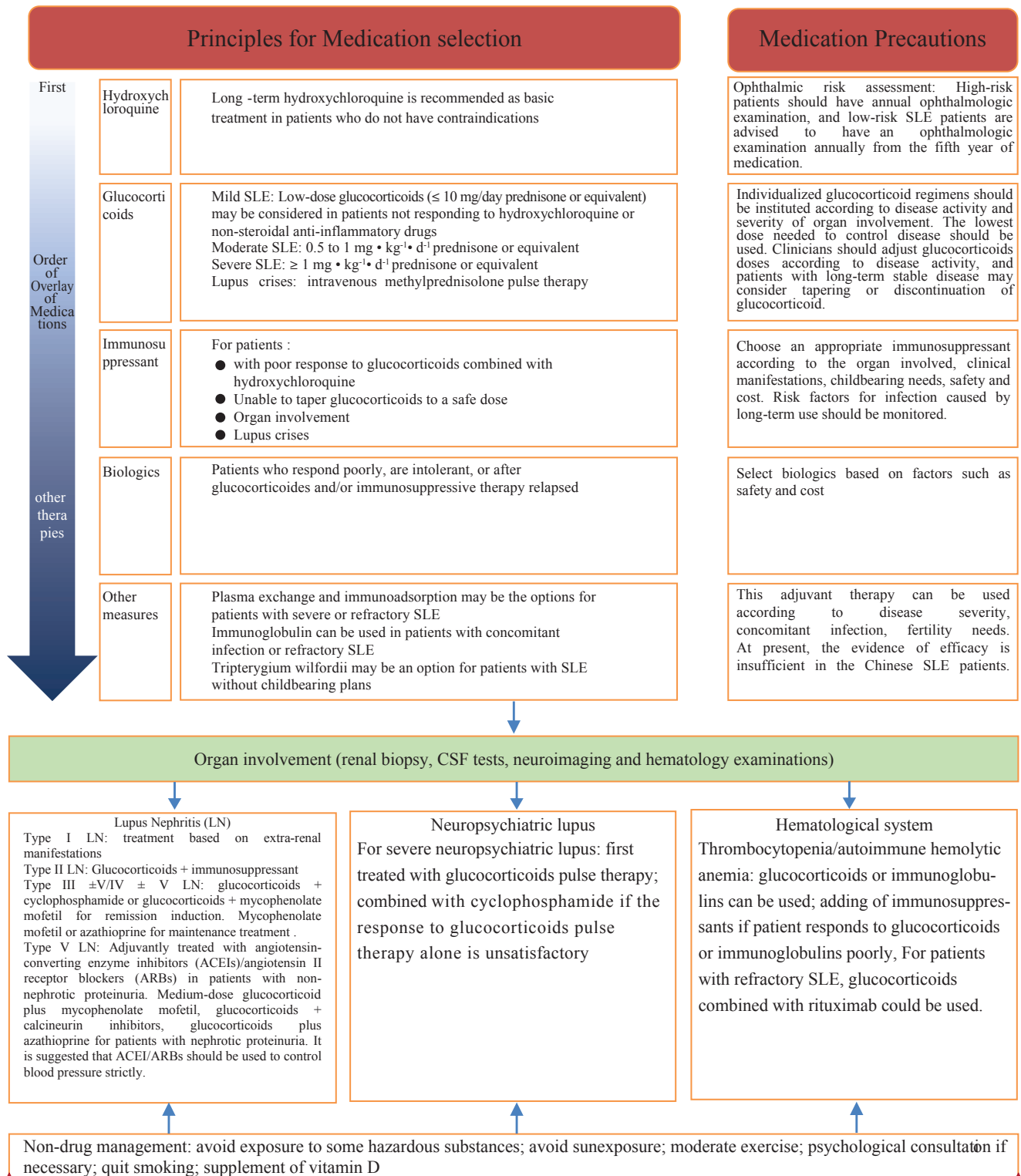


Figure 1: The diagnosis and treatment algorithm for systemic lupus erythematosus (SLE).

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Conflict of Interest

All authors declared that there was no conflict of interest.

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