Diagnosis and Management of Systematic Lupus Erythematosus (SLE)

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is the prototypic multisystem autoimmune disorder with a wide range of clinical presentations impacting almost all organs and tissues, such extreme heterogeneity suggests that SLE represents a syndrome rather than a single disease. Although the precise etiologic mechanism is unknown, genetic, hormonal, and environmental factors, as well as immune abnormalities, have been detected. Associations between lupus onset and age, sex, geography, and race have also been established.

Aim of the work: This review will focus on advances in the diagnosis and management of SLE.

Conclusion: The diagnosis of SLE must be based on the proper constellation of clinical findings and laboratory evidence. Management of this disease should be individualized and should include both pharmacological and non-pharmacological modalities for symptom relief and resolution as well as improved quality of life.

Keywords: Systematic Lupus Erythematosus, connective tissue disorder SLE, NSAID,

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune rheumatic disease with a highly variable course. It is most prevalent in females of childbearing age with a female: male ratio of 9:1 in this population. The prevalence of SLE is also higher in certain ethnicities, reflected in prevalence rates of 40/100 000 persons in Northern European cohorts in comparison with rates of 200/100 000 persons in studies of patients of African-American descent 1.

Patients with SLE may present with various systemic manifestations including diverse abnormalities of the skin, kidney, and haematological, pulmonary, and reproductive and musculoskeletal systems. The general symptoms are not specific. Common manifestations may include arthralgias and arthritis, malar and other skin rashes, pleuritis or pericarditis, renal or CNS involvement, hematologic cytopenias and weight changes are the most common symptoms in new cases or recurrent active SLE flares. Fatigue, the most common constitutional symptom associated with SLE, can be due to active SLE, medications, lifestyle habits, or concomitant fibromyalgia or affective disorders. Fatigue due to active SLE generally occurs in concert with other clinical and laboratory markers. Fever, another common yet nonspecific symptom of SLE, may also result from many causes, the most common of which include active SLE, infection, and drug fever. Careful history taking may help to differentiate these. Weight loss may occur in patients with active SLE. Weight gain may also be due to corticosteroid treatment or active disease such as nephrotic syndrome anasarca. These symptoms can mimic other autoimmune diseases, infectious diseases, endocrine abnormalities, chronic fatigue, and fibromyalgia. SLE significantly increases the risk of cardiovascular disease as well.

SLE a chronic, recurrent, potentially multisystem inflammatory which can be fatal and difficult to diagnose. The disease has no single diagnostic marker; instead, it is identified through a combination of clinical and laboratory criteria. Accurate diagnosis of systemic lupus erythematosus is important because treatment can reduce morbidity and mortality, particularly from lupus nephritis. This article reviews evidence-based recommendations for the diagnosis of systemic lupus erythematosus by primary care physicians. The 1992 Revised...
American College of Rheumatology (ACR) Classification Criteria however offers developed to aid trial design, offer a useful aide-mémoire to the rheumatologist of some of the more common features of SLE.

Management is complex and involves clinicians across many different specialties, with important variations in practice apparent across and within these specialties. For example, prescription of antimalarial drugs and testing for antiphospholipid antibodies are routine among rheumatologists but not among non-rheumatologists. Prescribed doses for glucocorticoid regimens also differ across specialties.

SLE is one of a small number of truly multisystem disorders. The heterogeneous nature of the disease can result in delayed diagnosis and cause considerable difficulty in the design of robust clinical trials. There is no diagnostic test specific for SLE and as such the diagnosis remains a clinical one, relying on a combination of clinical and laboratory features. The 1992 Revised American College of Rheumatology (ACR) Classification Criteria, while developed to aid trial design, offer a useful aide-mémoire to the rheumatologist of some of the more common features of SLE.

DIAGNOSIS OF SYSTEMATIC LUPUS ERYTHEMATOSUS (SLE)

The diagnosis of SLE is mainly done through:

1. **Clinical findings**: Close observation of the patients’ signs and symptoms.
   
The 1997 Update of the 1982 American College of Rheumatology (ACR) Revised Criteria for Classification of Systemic Lupus Erythematosus is a valuable resource in the assessment of patients when SLE is suspected. If a patient displays four or more of the 11 criteria (either simultaneously or at different time points), the diagnosis of SLE can be made with 95% specificity and 85% sensitivity.
   
   When the Systemic Lupus International Collaborating Clinics (SLICC) group revised and validated the ACR SLE classification criteria in 2012, they classified a person as having SLE in the presence of biopsy-proven lupus nephritis with ANA or anti-dsDNA antibodies or if 4 of the diagnostic criteria, including at least 1 clinical and 1 immunologic criterion, have been satisfied.

2. **Laboratory testing and evidence which is split into stages**:

   **Stage I: routine laboratory tests**, which probably provide first line diagnostically useful information
   
   i. Complete blood count and differential may reveal leukopenia, mild anemia, and/or thrombocytopenia
   ii. Elevated serum creatinine may be suggestive of renal dysfunction
   iii. Urinalysis with urine sediment may reveal hematuria, pyuria, proteinuria, and/or cellular casts

   **Stage II: SLE specific tests**

   1. **ANA testing**: positive in virtually all patients with SLE at some time in the course of their disease. If the ANA is positive, one should test for other specific antibodies such as dsDNA, anti-Sm, Ro/SSA, La/SSB, and U1 ribonucleoprotein (RNP). In some labs, a positive ANA test by indirect immunofluorescence will automatically result in testing for such additional antinuclear antibodies that are often present in patients SLE Anti-dsDNA and anti-Sm antibodies are highly specific for SLE, but anti-Sm antibodies lack sensitivity. Anti-dsDNA and anti-Sm antibodies are seen in approximately 70 and 30 percent of patients with SLE, respectively. 

   2. Anti-Ro/SSA and anti-La/SSB antibodies are present in approximately 30 and 20 percent of patients with SLE, respectively; however, both antibodies are more commonly associated with Sjögren’s syndrome.

   3. Anti-U1 RNP antibodies are observed in approximately 25 percent of patients with SLE, but they also occur in patients with other conditions and high levels are almost
always present in patients with mixed connective tissue disease (MCTD)\textsuperscript{13,14}.

4. Antiribosomal P protein antibodies have a high specificity for SLE, but have low sensitivity for SLE. They also lack specificity for involvement of a particular organ system or disease manifestation.

**Figure 1\textsuperscript{15}**: An algorithm for the diagnosis of systemic lupus erythematosus (SLE). (ANA = antinuclear antibody; ACR = American College of Rheumatology; anti dsDNA = antibody to double-stranded DNA antigen; anti-Sm = antibody to Sm nuclear antigen). Information source\textsuperscript{(11, 16, 17)}.

3- **Diagnostic testing tailored to each patient such as**:

a. Diagnostic imaging: not routinely obtained unless indicated by the presence of symptoms, clinical findings, or laboratory abnormalities. Examples include:
   - Plain radiographs of swollen joints. Unlike affected joints in RA, erosions are observed infrequently in SLE\textsuperscript{18}. Depending on the stage of disease, deformities may be present on radiograph.
   - Renal ultrasonography to assess kidney size and to rule out urinary tract obstruction when there is evidence of renal impairment.
   - Chest radiography (eg, for suspected pleural effusion, interstitial lung disease, cardiomegaly).
   - Echocardiography (eg, for suspected pericardial involvement, to assess for a source of emboli, or noninvasive estimation of pulmonary artery pressure; and for evaluation of suspected valvular lesions, such as verrucae).
   - Computed tomography (CT) (eg, for abdominal pain, suspected pancreatitis, interstitial lung disease).
   - Magnetic resonance imaging (MRI) (eg, for focal neurologic deficits or cognitive dysfunction).

b. Biopsy of an involved organ (eg, skin or kidney) is necessary in some cases. Typical histologic findings in various organs in SLE are discussed in topic reviews devoted to the particular sites of involvement.

c. Electrocardiography in the assessment of chest pain that may be due to pericarditis or to myocardial ischemia.

d. Tests to assess for pulmonary embolism in a patient with pleuritic chest pain and dyspnea.

e. Diffusing capacity for carbon monoxide (DLCO) to assess for suspected pulmonary hemorrhage and to estimate the severity of interstitial lung disease.

**MANGEMENT OF SYSTEMATIC LUPUS ERYTHEMATOSUS (SLE)**

The approach to the treatment of signs and symptoms of lupus depends on the type and the severity of disease. General recommendations for all patients include sun protection, proper diet and nutrition, exercise, smoking cessation, appropriate immunizations, and management of comorbid conditions.

\textit{A. Pharmacotherapy}
Medications used to treat SLE manifestations include the following:

1. **NSAIDs** may be used to alleviate musculoskeletal pain, swelling, and aches. These drugs possess pain-reducing, anti-inflammatory, and anticoagulant properties, which are beneficial in treating common lupus-associated manifestations; however, the potential for side effects (see Table 1) must be considered before clinicians prescribe NSAIDs for a patient with lupus.19,20

2. **Steroids:** Corticosteroids mimic naturally occurring hormones excreted by the adrenal gland and help regulate blood pressure and immune function. These agents decrease the swelling and pain associated with inflammation, which can occur in a lupus flare. Because of their serious long-term side effects (see Table 1), corticosteroids should be used at the lowest possible dose and only for periods necessary to control an active exacerbation of lupus.19,20

3. **Immunosuppressants** are primarily used in more severe cases of lupus when high-dose corticosteroids or antimalarial treatments have failed to control the signs and symptoms of disease. They are also used when it is necessary to induce and maintain remission and to reduce flares or relapses. Immunosuppressants may be given with high-dose corticosteroids to control flares, to achieve a lower dose of each medication, or to reduce the occurrence of adverse events. The most commonly used agents in this class are cyclophosphamide (Cytoxan, Bristol-Myers Squibb) and azathioprine (Azasan, Salix; Imuran, GlaxoSmithKline). Mycophenolate (CellCept, Genentech/Roche) has also been used for lupus-related kidney problems. Side effects of this drug class are listed in Table 1.19,20

4. **Antimalarial Medication:** Some antimalarial agents have proved effective in treating the various signs and symptoms of lupus and preventing subsequent flares. Although the exact mechanism is unclear (see Table 1), antimalarials may interfere with T-cell activation and inhibit cytokine activity. These agents may also inhibit intra-cellular toll-like receptors, which recognize and bind foreign materials, thereby contributing to activation of the immune system.21 Hydroxychloroquine (e.g., Plaquenil, Sanofi) is the most commonly studied and used drug in its class, but it has the potential to cause serious visual and muscle disturbances.

5. **Monoclonal Antibodies**
   - **“Belimumab”**

In March 2011, the FDA approved the first human monoclonal antibody for the treatment of lupus. Belimumab (Benlysta, Human Genome Sciences/GlaxoSmithKline) is the first agent in more than 50 years to be approved for patients with lupus. Belimumab inhibits the activation of B lymphocytes by interfering with a protein necessary for B-cell activity (BLYS). Previously known as LymphoStat-B, belimumab is recommended for patients with active SLE who are receiving standard therapy with NSAIDs, antimalarials, corticosteroids, and/or immunosuppressants. Common adverse effects are presented in Table 1.22

- **Rituximab**

As a genetically engineered chimeric monoclonal antibody directed against the CD20 antigen, rituximab (Rituxan, Genentech/Roche) has also shown potential in the treatment of SLE. It is believed that B cells responsible for the production of pathogenic autoantibodies, and other immune-mediated substances associated with lupus, are depleted by rituximab. During the past few years, a number of open-label and retrospective studies have reported promising results with rituximab (when taken with corticosteroids and other immunosuppressants in the management of both pediatric-onset and adult-onset lupus). Benefits of rituximab have also been noted in patients with lupus nephritis, arthralgia, arthritis, serositis, cutaneous vasculitis, mucositis, rashes, fatigue, and neurological and refractory symptoms. Adverse events were generally mild. Mild-to-moderate infusion reactions were reported most often.23,24

Some randomized controlled studies have provided mixed results regarding the efficacy and role of rituximab in the treatment of SLE. In a study by Terrier et al., clinical responses were reported in 71% of patients who received rituximab, demonstrating a significant benefit in refractory lupus (with or without concomitant immunosuppressive therapy). Cutaneous, articular, renal, and hematological improvements were noted most often, along with an acceptable tolerance profile.25

A systematic review covering 188 SLE patients treated with various regimens of rituximab, 91% showed a significant improvement in one or more systemic manifestations, particularly in patients with renal involvement (e.g., lupus nephritis). Adverse events were experienced by 23% of patients, and infections were reported most often.26 However, two additional randomized,
placebo-controlled studies, conducted since 2010, failed to demonstrate significant clinical improvements with rituximab in patients receiving concomitant steroid therapy. Despite the favorable tolerability and safety profile of rituximab, further evaluation of this drug is required for patients with SLE.

**Table 1: Commonly Used Medications in the Treatment of Systemic Lupus Erythematosus**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Commonly Used Agents and Dosage</th>
<th>Mechanism of Action</th>
<th>Potential Adverse Effects</th>
<th>Common Monitoring Parameters</th>
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</thead>
<tbody>
<tr>
<td><strong>NSAIDs (including salicylates)</strong></td>
<td>Prednisone PO 0.5–2 mg/kg per day</td>
<td>Block prostaglandin synthesis through inhibition of cyclooxygenase enzymes, producing anti-inflammatory, analgesic, and antipyretic effects</td>
<td>Gastrointestinal irritation and bleeding, renal toxicity, hepatic toxicity, hypertension</td>
<td>Nausea, vomiting, abdominal pain, dark/tarry stool; baseline and annual CBC, SCr, LFTs, urinalysis</td>
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<td></td>
<td>Methylprednisolone IV 500–1,000 mg daily for 3 to 6 days (acute flare)</td>
<td>Multiple effects on immune system (e.g., blocking cytokine activation and inhibiting interleukins, γ-interferon and tumor necrosis factor-α)</td>
<td>Weight gain, hyper tension, hyperglycemia, hyperlipidemia, osteoporosis, cataracts, edema, hypokalemia, muscle weakness, growth suppression, increased risk of infection, glaucoma</td>
<td>Baseline blood pressure, bone density, glucose, potassium, lipid panel; glucose every 3 to 6 months; annual lipid panel and bone density</td>
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<tr>
<td><strong>Corticosteroids</strong></td>
<td>Cyclophosphamide PO 1–3 mg/kg per day or 0.5–1 g/m² IV monthly with or without a corticosteroid</td>
<td>Multiple suppressive effect on immune system (e.g., reduction of T-cell and B-cell proliferation; DNA and RNA disruption)</td>
<td>Myelosuppression, hepatotoxicity, renal dysfunction, infertility, increased risk of infection and cancer</td>
<td>Baseline and routine CBC, platelet count, SCr, LFTs, and urinalysis (depends on individual drug)</td>
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<tr>
<td></td>
<td>Azathioprine PO 1–3 mg/kg per day</td>
<td>Block binding of BlyS to receptors on B cells, inhibiting survival of B cells, and reducing B-cell differentiation into immunoglobulin-producing plasma cells</td>
<td>Nausea, diarrhea, pyrexia, nasopharyngitis, insomnia, extremity pain, depression, migraine, gastroenteritis, infection (e.g., pneumonia, UTI, cellulitis, bronchitis)</td>
<td>Gastrointestinal complaints, infectious signs and symptoms, mood or behavioral changes, infusion reactions</td>
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<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td>Belimumab IV 10 mg/kg (over a period of 1 hour), every 2 weeks for the first three doses, then every 4 weeks</td>
<td>Unclear; may interfere with T-cell activation and inhibit cytokine activity; also thought to inhibit intracellular TLRs</td>
<td>Macular damage, muscle weakness</td>
<td>Funduscopy and visual field examination at baseline and every 6 to 12 months</td>
</tr>
<tr>
<td><strong>Antimalarials</strong></td>
<td>Hydroxychloroquine PO 200–400 mg daily</td>
<td>Nausea, vomiting, abdominal pain, dark/tarry stool; baseline and annual CBC, SCr, LFTs, urinalysis</td>
<td>Gastrointestinal irritation and bleeding, renal toxicity, hepatic toxicity, hypertension</td>
<td>Baseline and routine CBC, platelet count, SCr, LFTs, and urinalysis (depends on individual drug)</td>
</tr>
</tbody>
</table>
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BLyS = B-lymphocyte stimulator protein; CBC = complete blood count; DNA = deoxyribonucleic acid; IV = intravenous; LFTs = liver function tests; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = by mouth; RNA = ribonucleic acid; SCr = serum creatinine; TLRs = toll-like receptors; UTI = urinary tract infection.

B. Additional Treatment Options

Researchers have been particularly interested in the use of stem-cell transplantation to introduce healthy cells into the body in order to help rebuild the immune system. Both DHEA and rituximab have been studied in clinical trials and have provided improvements in patients’ quality of life. DHEA is believed to help in the regulation of sex hormones, whereas rituximab decreases the number of B cells and may be most beneficial in patients who do not respond to the other traditionally used immunosuppressants24,25.

C. Patient Education

Stress the importance of adherence to medications and follow-up appointments for detection and control of SLE disease. Instruct patients with SLE to seek medical care for evaluation of new symptoms, including fever. Advise them regarding their heightened risks for infection and cardiovascular disease. Educate patients with SLE regarding aggressive lipid and blood pressure goals to minimize the risk of coronary artery disease. Instruct patients with SLE to avoid exposure to sunlight and ultraviolet light. Also, encourage them to receive nonlive vaccines during stable periods of disease, to quit smoking, and to carefully plan pregnancies.

PREGNANCY

Women with SLE are at increased risk for serious medical and pregnancy complications, such as thrombosis, infection, thrombocytopenia, transfusion, pre-eclampsia, and death28. Because of the high risk of miscarriage, stillbirths, premature delivery, and exacerbation of SLE, it is recommended that women not become pregnant if they have active disease or significant organ involvement. Oral contraceptives must be given cautiously because high doses of estrogen can cause SLE exacerbations 28. Pregnancy outcomes are improved if conception is delayed until SLE has been inactive for at least 6 months and if the patient’s medications are adjusted in advance.

Baseline and monthly monitoring (e.g., laboratory tests, ultrasonography, fetal surveillance tests, maternal echocardiography, and antibody testing) should be performed for all pregnant lupus patients, because signs and symptoms of lupus flares may be similar to those typical of pregnancy28. Neonates should be carefully evaluated for placental transfer of maternal antibodies, which could lead to cutaneous or cardiac complications (e.g., congenital heart block and cardiomyopathy).

If a woman is pregnant and has active SLE, corticosteroids may be prescribed with caution to manage the disease. Most steroids are Pregnancy Category C drugs. NSAIDs (Pregnancy Category C and D) have also been used, but to a lesser extent, and they should be avoided during early pregnancy and the last trimester. If necessary, hydroxychloroquine may be used, but it is also a Pregnancy Category C drug. Therefore, therapy must be individualized and the drug’s benefits and risks must be carefully considered. Immunosuppressive agents are contraindicated in pregnancy, except for azathioprine, a Pregnancy Category C drug.

In women with SLE and antiphospholipid antibodies, prophylaxis with aspirin, low-molecular-weight heparin, or both, is indicated for the prevention of fetal loss28.

CONCLUSION

Although no cure has been discovered for this autoimmune disease, many medications are available to help control flares, to maintain remission, and to manage symptoms. Pharmacists and other health care professionals can play a vital role in treatment by educating patients, monitoring their therapeutic regimens, and identifying preventable drug-associated adverse events. Current research is under way, with the hope that improved quality of life and increased survival can be achieved for the many patients affected by SLE each year.

REFERENCES


