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# Modern Methods of Diagnosis and Treatment of Systemic Lupus Erythematosus

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**Abstract:** Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disorder with multiorgan involvement, characterized by impaired immunologic tolerance, B-cell hyperactivation, and activation of the interferon cascade. Contemporary diagnostic approaches include expanded immunologic profiling, molecular genetic studies, and the use of biomarkers of organ damage. SLE treatment is currently shifting from nonspecific immunosuppression toward personalized targeted therapy. The introduction of biologic agents and the treat-to-target strategy has substantially improved disease prognosis.

**Keywords:** Systemic lupus erythematosus, autoimmune disease, antinuclear antibodies, EULAR/ACR 2019 criteria, lupus nephritis, interferon signature, targeted therapy, biologic agents, treat-to-target, immunologic biomarkers.

## Relevance

SLE remains one of the most complex nosologic entities in rheumatology due to:

- heterogeneity of clinical manifestations
- the absence of a specific diagnostic test
- the high risk of lupus nephritis
- complications associated with immunosuppressive therapy

Conventional therapy with glucocorticosteroids and cytotoxic agents is associated with serious adverse effects, which has stimulated the development of targeted drugs with more selective mechanisms of action.

**Introduction:** Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease of unknown etiology with a broad spectrum of clinical manifestations and an unpredictable course. Serologically, SLE is characterized by high titers of non-organ-specific autoantibodies directed against various components of the cell nucleus. Both innate and adaptive immune responses are involved in SLE pathogenesis. The interaction between genetic factors and environmental influences leads to numerous immunologic alterations, resulting in immune responses against autologous nucleic acids. Autoantibodies and immune complex deposition may damage tissues in the kidneys, heart, blood vessels, central nervous system, skin, lungs, muscles, and joints.

## METHOD

### Challenges in the Diagnosis of Systemic Lupus Erythematosus

The differential diagnosis of SLE and other conditions should be based on careful history taking, detailed clinical examination, the use of the necessary laboratory and instrumental diagnostic methods, and standardized criteria (Table 1).

**Table 1. Diseases Included in the Differential Diagnosis of SLE**

| Diseases | | | Therapeutic-agents |
|---|---|---|---|
| **Immune-inflammatory** | **Infectious** | **Neoplastic** | |
| • Sjögren's Syndrome<br>• Dermatomyositis<br>• APS<br>• Undifferentiated arthritis<br>• Systemic vasculitides<br>• Macrophage activation syndrome<br>• Autoimmune hemolytic anemia<br>• Idiopathic thrombocytopenic purpura<br>• Thrombotic thrombocytopenic purpura<br>• Sarcoidosis<br>• Fibromyalgia<br>• Autoimmune hepatitis<br>• Autoimmune thyroiditis | *Viral:*<br>• Parvovirus B19<br>• CMV<br>• HIV<br>*Bacterial:*<br>• Treponem a pallidum<br>• Borrelia burgdorferi<br>*Fungal:*<br>• Trichophyton infection<br>*Parasitic:*<br>• Toxoplasma spp | • Kikuchi disease<br>• Castleman disease<br>• T- and B-cell lymphomas<br>• Chronic leukemias<br>• Plasmacytomas | • TNF-alpha inhibitors<br>• IFN-alpha<br>• Vaccination |

Abbreviations: APS - antiphospholipid syndrome, CMV - cytomegalovirus, HIV - human immunodeficiency virus, TNF-alpha - tumor necrosis factor-alpha, IFN-alpha - interferon-alpha

The diagnosis of systemic lupus erythematosus (SLE) is associated with a number of objective challenges.

First, although very rarely, ANA-negative variants of the disease do occur. Second, at the initial stage of the disease, a patient may lack a sufficient number of clinical and laboratory features required for formal confirmation of the diagnosis.

According to the 2019 European League Against Rheumatism / American College of Rheumatology criteria, a positive antinuclear antibody (ANA) test is a mandatory entry criterion. This is a fundamental difference from earlier classifications. A negative ANA result within these criteria formally excludes SLE.

Nevertheless, the clinician must take concomitant pathology into account. An elevated ANA titer combined with at least one of the following signs - arthritis or arthralgia, skin rash, alopecia, Raynaud phenomenon, serositis, or sicca syndrome - may suggest disease onset or a high risk of developing an autoimmune rheumatic disorder.

The reverse situation also requires caution. A positive ANA in the absence of clinical symptoms is more often associated with other conditions, including autoimmune thyroiditis, chronic viral hepatitis, drug exposure, or asymptomatic carriage. According to published data, ANA is detected in up to 20% of healthy individuals at a titer of >=1:80. At SLE onset, a normal ANA level is extremely rare (less than 5%), and later it is observed in 5-20% of cases, which may be related to intensive therapy or methodological features of laboratory testing.

A number of publications have proposed raising the diagnostic threshold for ANA positivity from >=1:80 to >1:160 in order to increase criterion specificity. This approach is justified because titers >1:160 are detected much less frequently in the general population.

It is important to remember that the EULAR/ACR 2019 criteria are classificatory in nature and do not constitute an absolute diagnostic algorithm. In exceptional cases, when characteristic clinical and immunologic features are present despite a negative ANA, hypocomplementemia or the presence of antiphospholipid antibodies may be used for orientation. An alternative is the 2012 Systemic Lupus International Collaborating Clinics criteria, in which a positive ANA test is not a mandatory requirement.

Another feature of the 2019 criteria is the differentiated weighting of the diagnostic significance of each finding. The highest weight (6-10 points) is assigned to histologically confirmed lupus nephritis, acute pericarditis, synovitis involving two or more joints, acute cutaneous lupus, and positivity for anti-dsDNA and anti-Sm. This approach facilitates early

diagnostic verification: with a positive ANA, the presence of one highly weighted feature (for example, class III-IV nephritis) or a combination of several criteria allows SLE to be established.

In patients with early-stage disease, the EULAR/ACR 2019 criteria demonstrate higher specificity and fewer false-positive results than previous systems. In practice, it is reasonable to use the EULAR/ACR 2019 and SLICC 2012 criteria in parallel in order to minimize diagnostic errors at an early stage.

**Practical Aspects of Diagnosis and Monitoring**

Several principles should be considered in clinical practice:

- repeat ANA testing after positivity has already been confirmed has no diagnostic value;
- when disease activity is low or remission has been achieved, frequent monitoring of specific serologic markers is unnecessary;
- regular urinalysis is an essential component of follow-up for the early detection of nephritis;
- not every symptom in a patient with established SLE should automatically be interpreted as a manifestation of the disease - infections, neoplasms, and other independent causes must be excluded.

SLE is particularly insidious because of its variability. At times it is overt and dramatic, while at other times it remains masked for years. Therefore, clinical reasoning is more important here than blind adherence to a table of criteria. In rheumatology, the mechanical use of checklists rarely resolves the problem.

**Contemporary Treatment of Systemic Lupus Erythematosus**

Contemporary therapy for systemic lupus erythematosus (SLE) is based on the principles of early treatment initiation, risk stratification, objective assessment of disease activity, and implementation of the treat-to-target strategy aimed at achieving remission or sustained low disease activity. The main therapeutic goals are suppression of the immune-inflammatory cascade, prevention of target-organ damage, minimization of glucocorticoid burden, and reduction of the risk of exacerbations and drug-related complications.

Basic therapy. Hydroxychloroquine is recommended for most patients with SLE in the absence of contraindications and is regarded as the foundation of treatment. The drug reduces the frequency of exacerbations, decreases the risk of thrombotic complications, exerts a cardioprotective effect, and is associated with improved overall survival. Long-term use requires regular ophthalmologic monitoring to prevent retinopathy.

Glucocorticosteroids. Glucocorticosteroids (GCS) remain an important component of treatment, especially in patients with high disease activity and involvement of vital organs. The current strategy implies the use of the minimum effective doses followed by rapid tapering, which reduces the risk of steroid-induced complications. Pulse therapy with methylprednisolone is used in severe conditions, including lupus nephritis, neuropsychiatric lupus, and autoimmune cytopenias.

Immunosuppressive therapy. The choice of an immunosuppressive agent is determined by the pattern of organ involvement and the degree of disease activity. Mycophenolate mofetil is a first-line agent for class III-V lupus nephritis. Cyclophosphamide is used in life-threatening forms and severe systemic manifestations. Azathioprine is used mainly for maintenance therapy, whereas methotrexate is indicated in pronounced articular syndrome. Treatment regimens are selected individually, taking into account the patient's age, comorbidities, and reproductive plans.

Biologic therapy. The transition to targeted treatment has become a key stage in the evolution of SLE management. The BLyS inhibitor belimumab reduces B-cell activity and the frequency of exacerbations, thereby helping to decrease steroid dependence. The type I interferon receptor blocker anifrolumab is effective in patients with a pronounced interferon signature. Rituximab is used in refractory forms and severe organ involvement. Targeted therapy makes it possible to selectively influence key links in pathogenesis and to reduce systemic immunosuppression.

Treatment of lupus nephritis. Lupus nephritis remains one of the most prognostically significant complications of SLE. Therapy includes an induction phase (mycophenolate or cyclophosphamide in combination with glucocorticosteroids) and a maintenance phase (mycophenolate or azathioprine). An important component is the control of proteinuria and arterial pressure using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Early kidney biopsy makes it possible to determine the morphologic class of nephritis and optimize therapeutic tactics.

Personalized approach. Modern rheumatology is focused on treatment personalization. The SLEDAI activity index, monitoring of anti-dsDNA and complement levels, stratification according to interferon signature, and molecular genetic markers are used. Individualization of therapy helps reduce the

frequency of severe exacerbations, limit excessive immunosuppression, and improve long-term prognosis.

**Prognosis**

Over recent decades, the 10-year survival of patients with SLE has increased substantially and exceeds 85-90% in developed countries. Unfavorable prognostic factors include lupus nephritis, central nervous system involvement, antiphospholipid syndrome, delayed diagnosis, and poor adherence to therapy. Early diagnostic verification and adequate targeted therapy substantially alter the natural course of the disease and improve patients' quality of life.

## CONCLUSION

Systemic lupus erythematosus remains a complex multisystem disease with a variable course and diverse clinical manifestations. Modern diagnostic criteria, expanded immunologic methods, and the use of biomarkers make it possible to verify the diagnosis more accurately at early stages.

In SLE management, a transition is being observed from nonspecific immunosuppression to personalized targeted treatment. The use of biologic agents and the treat-to-target strategy contributes to reduced disease activity, fewer exacerbations, and improved quality of life.

Thus, advances in molecular immunology and pharmacotherapy are opening new prospects in the treatment of SLE, shaping a more predictable and controllable model of patient management.

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